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EFFECT OF CHOLECYSTOGASTROSTOMY ON CINCHOPHEN-PRODUCED ULCER IN DOGS

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The role played by the digestive juices in the causation of peptic ulcer has long been under investigation. The acid "gastric chyme" has been studied by a variety of methods, and from the results obtained many investigators have delegated to it the role of villain in the drama of the pathogenesis of ulcer. From this point of view, interest was aroused in possible mechanisms or substances which might normally "protect" against ulcer formation. Among these, attention has been centered on the alkaline digestive juices—the succus entericus, the pancreatic juice and the bile. Attempt has been made to evaluate the "protective" qualities of these secretions *in toto,* singly and in various combinations.

Most previous work has been done by means of the Mann-Williamson preparation, whereby "duodenal drainage" is instituted and then single or combined alkaline juices are reshunted to the upper part of the intestinal tract in an attempt to evaluate their "protective" action. Recently, however, a new method of producing chronic gastric ulcers experimentally in dogs was discovered by Churchill and Van Wagoner.[1] This is accomplished by daily administration of old cinchophen, which results in a very high incidence of gastric ulcers closely simulating those seen clinically in man. This method has the advantage of not introducing a surgical procedure or altering the normal continuity of the gastrointestinal tract in the production of the ulcers.

This newer technic suggested itself to me as another method whereby the "protective" influence of the alkaline juices might be evaluated, and this paper is a report of the experimental investigation of one of these juices, i. e., the bile.

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1. Churchill, T. P., and Van Wagoner, F. H.: Cinchophen Poisoning, Proc. Soc. Exper. Biol. & Med. **28**:581, 1931. Van Wagoner, F. H., and Churchill, T. P.: Production of Gastric and Duodenal Ulcers in Experimental Cinchophen Poisoning: Preliminary Report, J. A. M. A. **99**:1859 (Nov. 26) 1932.

REVIEW OF LITERATURE

The attempt to produce chronic ulcer in experimental animals has long engaged the attention of many investigators throughout the world, and a variety of technics have been involved which produced ulcerations in various laboratory animals. These experiments have been reviewed in detail by McCann.[2] Although a great variety of methods produced ulcerations in many different animals, it was apparent that none of these technics gave consistent results, that the ulcers were chiefly acute lesions which tended to heal rapidly and hence were in no wise similar to the chronic indurated lesion observed in man and that only certain animals, especially dogs, have gastric mucosa which behaves enough like that of the human being to make them valuable as experimental subjects. That a great variety of factors may initiate gastric or duodenal ulceration seems clear from these experiments, but the real problem, "the circumstance that it usually so obstinately refuses to heal," as Cohnheim stated in 1880, was not approached.

In 1923, however, Mann and Williamson [3] demonstrated a method whereby chronic indurated ulcers might be produced in a high percentage of dogs. This procedure, anastomosis of the stomach to the jejunum with "drainage" of the intervening duodenum into the lower part of the small bowel, had been previously done in effect by Bickel [4] in 1909 and by Langenskiöld [5] in 1914, but these authors had not followed up their observations, and their conclusions were not generally adopted. After the clear demonstration by Mann and Williamson [3] of the value of this technic an era of intense experimentation was begun. Morton [6] McCann,[7] Gallagher and Palmer,[8] Jenkins and Palmer [9] and Matthews

2. McCann, J. C.: Experimental Peptic Ulcer, Arch. Surg. **19**:600 (Oct.) 1929.

3. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1923.

4. Bickel, A.: Beobachtungen an Hunden mit extirpiertem Duodenum, Berl. klin. Wchnschr. **46**:1201, 1909.

5. Langenskiöld, F.: Ueber die Widerstandsfähigkeit einiger lebender Gewebe gegen die Einwirkung eiweisspaltender Enzyme, Skandinav. Arch. f. Physiol. **31**:1, 1914.

6. Morton, C. B.: Observations on Peptic Ulcer: I. A Method of Producing Chronic Gastric Ulcer; a Consideration of Etiology, Ann. Surg. **85**:207 and 879, 1927; III. Healing of Experimentally Produced Ulcer After Gastro-Enterostomy, ibid. **85**:729, 1927; V. Findings in Experimentally Produced Peptic Ulcer: Etiologic and Therapeutic Consideration, ibid. **87**:401, 1928.

7. McCann, J. C.: Control of Acidity, Am. J. Physiol. **89**:483, 1929; footnote 2.

8. Gallagher, W. J., and Palmer, W. L.: Experimental Jejunal Ulcer: Relative Importance of Mechanical and Chemical Factors, Proc. Soc. Exper. Biol. & Med. **30**:468, 1932.

9. Jenkins, H. P., and Palmer, W. L.: Studies on Experimental Jejunal Ulcers, Proc. Soc. Exper. Biol. & Med. **28**:935, 1931.

and Dragstedt,[10] to mention only a few of the investigators, confirmed the value of the method. It was felt by most of these authors that two factors are important in the establishment of the ulcers: (1) the acid gastric chyme acting unneutralized on the jejunal mucosa and (2) the mechanical force of the ejected stream of chyme impinging against the jejunal wall.

This work stimulated an interest in the protective action of the duodenal juices and gave an experimental method whereby they might be studied. Bile has received particular attention in this regard.

The composition of bile varies considerably in different species and within the same species. However, its p_H has been stated by Horrall [11] to vary between 5.7 and 7.86, while that of hepatic bile was said by Jones [12] to lie between 7.4 and 8.5. Boldyreff [13] found the alkalinity of bile to be equivalent to only 0.05 per cent sodium carbonate. However, despite its low actual alkalinity, it has been felt that its buffering capacity is high.

It was first noticed by Hooper and Whipple [14] that a large percentage of dogs with external biliary fistulas had peptic ulcers. Thus it seemed that loss of bile alone from the duodenum resulted in a fair incidence of duodenal ulcers. Kapsinow [15] criticized the interpretation of this work on the basis that infection ascending the fistulous tract might be an important factor. He therefore performed cholecystonephrostomy on 43 dogs, in 17 of which chronic duodenal ulcers developed. Neumann and his co-workers [16] diverted the bile to the ileum and produced 5 ulcers in 7 dogs. They repeated the experiment on 2 additional series and got similar results. Weiss and Gurriaran [17] observed one ulcer in 3 fistulous

10. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **55**:265, 1932.

11. Horrall, O. H.: Bile: Its Toxicity and Relation to Disease, Chicago, University of Chicago Press, 1938.

12. Jones, K. K.: Comparison of Buffer Value of Bile and Pancreatic Juice Secreted Simultaneously, Proc. Soc. Exper. Biol. & Med. **28**:567, 1931.

13. Boldyreff, W.: The Self Regulation of the Acidity of the Gastric Contents and the Real Acidity of the Gastric Juice, Quart. J. Exper. Physiol. **8**:1, 1915.

14. Hooper, C. W., and Whipple, C. H.: Bile Pigment Output and Diet Studies, Am. J. Physiol. **40**:332, 1916.

15. Kapsinow, R.: The Experimental Production of Duodenal Ulcer by Exclusion of Bile from the Intestine, Ann. Surg. **83**:614, 1926.

16. Neumann, F.; Demoor, P., and Deloyers, L.: Contributions à l'étude de la pathogénie des ulcères gastroduodénaux: Dérivation exclusive de la bile dans l'iléon terminal, Compt. rend. Soc. de biol. **105**:890, 1931.

17. Weiss, A. G., and Gurriaran, G.: Ulcères chroniques gastroduodénaux expérimentaux crées par la dérivation des sucs alcalins duodénaux, Bull. et mém. Soc. nat. de chir. **36**:6, 1930.

dogs, Owings and Smith [18] two in 5, and Graves [19] one in 8. Bachrach and others [20] observed two ulcers in 15 dogs. Berg, Johnston and Jobling [21] observed the incidence of ulcer in Rous-McMaster fistulous dogs to be 77 per cent. These and other demonstrations indicated that "exclusion of the liver," by whatever means, is followed by the occurrence of duodenal ulcers in a percentage of the animals. However, this percentage varied greatly in the hands of different workers and with different technics. Moreover, it was not clear whether the lesions arose because of the lack of bile as a "protective" substance in the duodenum or were associated with the profound metabolic changes which occurred in the fistulous dogs. Berg and his associates found that a larger percentage of dogs receiving poor diet and living in a poor environment had ulcers than of dogs with a better hygienic regimen, and Ivy [22] and others have also emphasized that cachexia is an important predisposing factor in experimental ulcer.

Blanck [23] stated that in all of 5 dogs with biliary fistula duodenal ulcers were obtained, while of 3 others which were refed the bile obtained from the fistula only 1 had an ulcer. Bachrach and his co-workers [20] have criticized this work, however, pointing out that the series was small and the time of survival too short. These authors were able to obtain only two duodenal ulcers in 15 fistulous dogs, and Graves [19] pointed out that Rous and McMaster, Elman, and Puestow found no ulcers in their experiments with fistula.

To attempt to evaluate the actual local protective value of bile, Ochsner and his associates [24] made a gastric pouch and anastomosed the jejunum to the pouch. Ulcers formed in the adjacent jejunum in 85 per cent of cases. If they also anastomosed the gallbladder to the pouch, only 39 per cent of the animals had ulcers. DeBakey [25] performed pyloric exclusion with anterior gastroenterostomy in 20 dogs. Fifty per cent had jejunal ulcer. If he also diverted the bile by anastomosing

18. Owings, J. C., and Smith, I. H.: Experimental Production and Cure of Jejunal Ulcers, Proc. Soc. Exper. Biol. & Med. **29**:837, 1932.

19. Graves, A. M.: Combined and Separate Effects of Bile, Pancreatic Secretion and Trauma in Experimental Peptic Ulcer, Arch. Surg. **30**:833 (May) 1935.

20. Bachrach, W. H.; Schmidt, C. R., and Beazell, J. M.: The Relation of Bile and Pancreatic Juice to Duodenal Ulcer in Dogs, Proc. Soc. Exper. Biol. & Med. **40**:322, 1939.

21. Berg, B. N.; Johnston, A., and Jobling, J. W.: Duodenal and Gastric Ulcers in Dogs with Biliary Fistulae, Proc. Soc. Exper. Biol. & Med. **25**:334, 1928.

22. Ivy, A. C.: Studies on Gastric and Duodenal Ulcer, J. A. M. A. **75**:1540 (Dec. 4) 1920.

23. Blanck, E. E.: Peptic Ulcer, Surg., Gynec. & Obst. **61**:480, 1935.

24. Ochsner, A.; Gage, M., and Hosoi, K.: The Relationship of Peptic Ulceration to Gastric Chemism, Proc. Soc. Exper. Biol. & Med. **31**:1260, 1934.

25. DeBakey, M. E.: Peptic Ulceration: The Relative Protective Value of the Alkaline Duodenal Juices, Arch. Surg. **34**:230 (Feb.) 1937.

the common duct to the ileum, 90 per cent had ulcers. These authors concluded, therefore, that bile has a definite local protective value. That its presence alone in the jejunum of a Mann-Williamson dog is inadequate to protect against ulcer formation was shown by Graves, who did "duodenal drainage" and then anastomosed the common duct to the jejunum. In 5 of his 6 animals the usual ulcers developed. Likewise, Neuman and his associates,[26] who performed a similar operation except that they anastomosed the gallbladder to the jejunum, obtained ulcers in 2 of 5 dogs.

The introduction by Van Wagoner and Churchill in 1932 of the cinchophen method of producing gastric ulcer in dogs has opened a new avenue of approach in the experimental study of ulcer. By feeding old cinchophen to dogs over a long period, chronic indurated ulcers, located chiefly in the stomach, were produced in a large percentage of animals. This work was soon confirmed by Bollman and Mann [27] and Barbour and Fisk.[28] Early gastritis occurs, which clears up, leaving a single or, rarely, a double chronic indurated lesion almost invariably situated on the lesser curvature of the stomach, just above the pylorus. Schwartz and Simonds [29] observed that chronic ulcer was developed by this method in cats and dogs but not in rabbits and guinea pigs. Churchill and Manshardt [30] found that gastric ulcers resulted even if the drug was administered into an isolated loop of intestine. Hanke [31] found that use of the subcutaneous route resulted in ulcerations in the stomachs of cats. Stalker, Bollman and Mann [32] stated that ulcer will result

26. Neumann, F.; Demoor, P., and Deloyers, L.: Contribution à l'étude de la pathogénie des ulcères duodénaux. Dérivation des sucs duodénaux et pancréatiques dans l'iléon terminal, Compt. rend. Soc. de biol. **105**:892, 1931.

27. Bollman, J. L., and Mann, F. C.: Experimental Production of Gastric Ulcers, Proc. Staff Meet., Mayo Clin. **10**:580, 1935.

28. Barbour, H. G., and Fisk, M. E.: Liver Damage in Dogs and Rats After Repeated Oral Administration of Cinchophen, J. Pharmacol. & Exper. Therap. **48**:341, 1933.

29. Schwartz, S. O., and Simonds, J. P.: Peptic Ulcers Produced by Feeding Cinchophen to Mammals Other than the Dog, Proc. Soc. Exper. Biol. & Med. **32**: 1133, 1935.

30. Churchill, T. P., and Manshardt, D. D.: Experimental Production of Gastric and Duodenal Ulcers in Dogs in Cinchophen Poisoning, Proc. Soc. Exper. Biol. & Med. **30**:825, 1933.

31. Hanke, H.: Ueber experimentelle akute Atophanylgastritis als Erscheinungform einer vorwiegend toxisch bedingten Gastritis, Beitr. z. path. Anat. u. z. allg. Path. **94**:313, 1934.

32. Stalker, L. K.; Bollman, J. L., and Mann, F. C.: Experimental Peptic Ulcer Produced by Cinchophen: Methods of Production, the Effect of a Mechanical Irritant, and the Life History of the Ulcer, Arch. Surg. **35**:290 (Oct.) 1937. Bollman, J. L.; Stalker, L. K., and Mann, F. C.: Experimental Peptic Ulcer Produced by Cinchophen, Arch. Int. Med. **61**:119 (Jan.) 1938. Stalker, L. K.; Boll-

(Footnote continued on next page)

whether the drug is administered by rectum, subcutaneously, intravenously, into an isolated intestinal loop or by mouth. The total gastric secretion was found by these authors to increase twofold or threefold during cinchophen administration, but there was no increase in the acidity. If the prepyloric area was excised, ulcers appeared in the jejunum in 40 per cent of the animals.

Pathologically, such ulcers closely resemble those seen in man and those obtained by the "duodenal drainage" method of Mann and Williamson. Simonds [33] and also Bollman, Stalker and Mann have described the development of the ulcer in two stages. The primary stage lasts a week or ten days; there are acute diffuse gastritis with edema of the mucosa, plasma cell and lymphocytic infiltration, small hemorrhagic erosions and small fistulous channels in the mucosa containing polymorphonuclear leukocytes. The secondary stage consists of return to normal of most of the stomach but, at the same time, progression of one of the early erosions to a deep chronic ulceration in the prepyloric region, with a necrotic, inflamed base and indurated walls. Lesions of this type extend far into the muscularis and, indeed, may perforate or cause massive hemorrhage by erosion of a blood vessel. They heal in a manner entirely similar to that described by Mann [34] for ulcers produced by "duodenal drainage" and by Caylor [35] for ulcers in human beings. A few days after cessation of cinchophen therapy the necrotic material at the base disappears; clean granulation tissue forms, and the ulcer granulates in from the bottom up. Except for a period of acute toxicity, when there is moderate cloudy swelling in the liver and kidneys, no damage to the liver is noted even after prolonged administration of the drug, and no other pathologic changes in other organs are observed.

Diet during the administration of cinchophen appears to have a definite relation to the formation of the ulcers. Thus Stalker and his co-workers [36] found that coarse food hastened the formation of ulcers, while a milk diet delayed them and produced subacute ulcers. If alkalis and a soft diet were given, no ulcers appeared. Likewise, Reid and Ivy [37] found that if 30 Gm. of gastric mucin was given three times a day

man, J. L., and Mann, F. C.: Effect of Cinchophen on Gastric Secretion: An Experimental Study, Arch. Surg. **34**:1172 (June) 1937.

33. Simonds, J. P.: Mode of Origin of Experimental Gastric Ulcer Produced by Cinchophen, Arch. Path. **26**:44 (July) 1938.

34. Mann, F. C.: Production and Healing of Peptic Ulcer: An Experimental Study, Minnesota Med. **8**:638, 1925.

35. Caylor, H. D.: Healing of Ulcer in Man, Ann. Surg. **83**:350, 1926.

36. Stalker, L. K.; Bollman, J. L., and Mann, F. C.: Prophylactic Treatment of Peptic Ulcers Produced Experimentally by Cinchophen, Am. J. Digest. Dis. & Nutrition **3**:822, 1937.

37. Reid, P. E., and Ivy, A. C.: Gastric Mucin a Prophylactic Against Gastro-Duodenal Ulcers and "Acute" Toxicity Resulting from Cinchophen, Proc. Soc. Exper. Biol. & Med. **34**:142, 1936.

to dogs receiving cinchophen, only 18 per cent had ulcers in eighty days, while 100 per cent of the controls had ulcers in from seven to fifty-nine days.

Thus it can be seen that, although the reason for the development of the cinchophen ulcer is not clear, the lesion is pathologically similar to that seen in man, and its response to alkaline diet therapy is likewise parallel.

METHOD

Two series of dogs were studied. In one group cholecystogastrostomy was performed, with ligation and division of the common duct. After recovery from the operation, administration of cinchophen was begun, and the course was observed. The other group served as controls, and addition of cinchophen to the diet was the only procedure employed. Both groups were fed the same diet, a commercial ground meal preparation, and enjoyed identical living conditions and general care.

The animals were unselected, healthy laboratory dogs which varied in weight from 7 to 23 Kg. Old cinchophen, obtained from Sharp and Dohme, was given in doses of 150 to 200 mg. per kilogram of body weight five days a week. In some instances the dogs took the drug in pill form, embedded in a small meat ball; in other cases it was necessary to give it in capsules.

The operative technic closely followed that outlined by Walters.[38] With the dog under intravenous pentobarbital sodium anesthesia, an incision was made just to the right of the midline, the rectus muscle being retracted laterally. The common duct was identified, doubly ligated above and below and severed. The gallbladder was then mobilized by blunt dissection from its hepatic bed. Oozing was controlled by hot packs. The fundus of the gallbladder was then anastomosed to the anterior wall of the stomach 2½ to 3 inches (6.2 to 7.6 cm.) above the pylorus. The stoma was about 2 cm. in length and was closed with three suture lines of fine silk: a mucosa to mucosa Connell suture, a continuous muscularis and serosa suture and a peripheral serosa to serosa suture. One or two stay sutures were placed to hold the omentum around the anastomosis. Hemostasis was easily accomplished except for moderate bleeding from the muscularis of the gallbladder. No intestinal clamps were employed. The wound was closed with silk in most cases, although no. 1 chromic catgut was occasionally used on the peritoneum. A subcuticular skin suture was employed, and the wound was left without dressing. Postoperative care consisted of giving an ample supply of water, no food by mouth for twenty-four hours, milk diet for two days and then a soft solid diet for five days. At the end of the first week most of the dogs seemed completely recovered, and they were then returned to their runways. Administration of cinchophen was sometimes begun as early as the tenth or twelfth postoperative day.

The control series of animals comprised 8 dogs. A summary of the protocols of these dogs is given to show the variations in the response to cinchophen of the normal animal.

PROTOCOLS

Dog 1.—A dog weighing 5.1 Kg. died five days after administration of cinchophen was begun.

Gross Observations.—There were marked emaciation, hemorrhagic gastritis and enteritis, with hemorrhage into the intestinal tract.

38. Walters, W.: Cholecystogastrostomy, Surg., Gynec. & Obst. **42**:825, 1926.

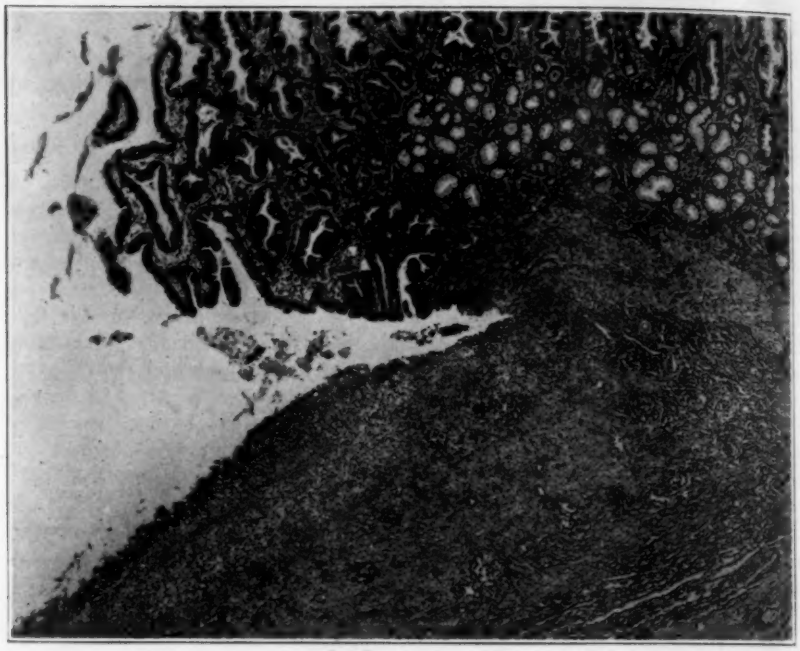

Fig. 1 (dog 2).—Photomicrograph of the margin of a gastric ulcer, showing the overhanging mucosa and the indurated edge. × 41.

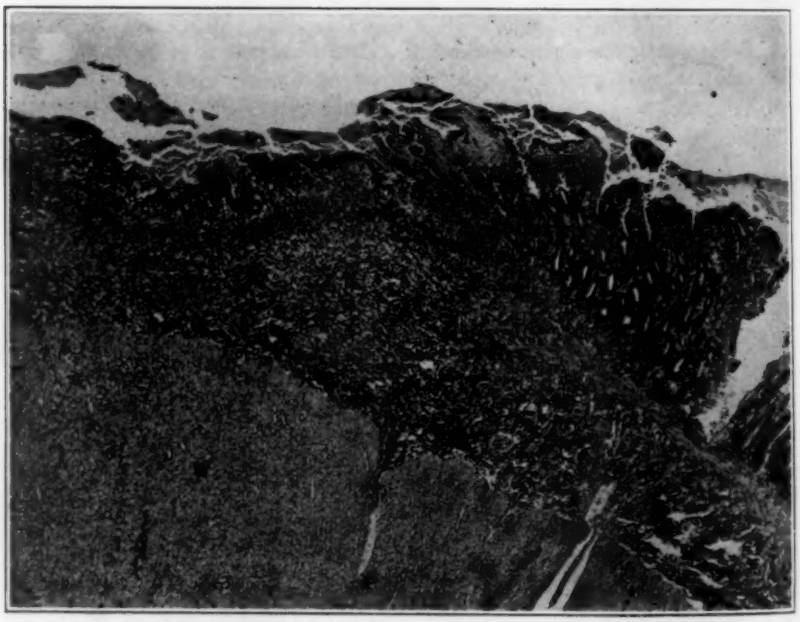

Fig. 2 (dog 2).—Photomicrograph of the margin of an ulceration of the ileum, showing destruction of the mucosa, extension through the muscularis mucosae and marked inflammation. × 41.

Microscopic Observations.—The gastric ulcerations were multiple and small and extended to involve the muscularis mucosae. The mucosa was destroyed in these areas; much brown pigment was present, and the base showed definite leukocytic infiltration. There were small ulcerations of the ileum, extending down to but not involving the muscularis mucosae. The liver cells showed cloudy swelling. The renal tubules showed cloudy swelling and contained hyaline droplets in their lumens.

Dog 2.—A lanky dog weighing 9 Kg. died on the thirteenth day of administration of cinchophen. Autopsy was performed about ten minutes post mortem.

Gross Observations.—The dog was emaciated. The stomach showed a small, deep ulcer just above the pylorus, on the lesser curvature. There were many ulcerations throughout the small bowel, with gross hemorrhage into the intestinal tract.

Microscopic Observations.—The gastric ulcer showed sharp, undermined edges, with induration; the base was composed of necrotic tissue, fibrin, connective tissue and leukocytes. It extended well through the muscularis mucosae. The ulcers in the jejunum and ileum extended through to the muscle wall. Their base consisted of partially necrotic, inflamed granulation tissue. The mucosa was entirely destroyed. Strands of inflammatory leukocytes extended deep into the muscularis along the perivascular lymphatics. Masses of mixed bacteria were seen on the surface of the ulcers. The colonic mucosa showed a diffuse surface inflammation. The vessels were congested; acute leukocytic infiltration was seen, and the superficial third of the mucosa showed necrotic changes. Masses of bacteria were seen clinging to the surface. The renal tubules showed cloudy swelling, and many of the cells contained masses of brown pigment.

Dog 3.—A dog weighing 7.4 Kg. died rather suddenly on the fourteenth day of cinchophen treatment.

Gross Observations.—The peritoneal cavity contained gross blood. The stomach contained a deep, punched-out, perforated gastric ulcer 1 cm. in diameter in the lesser curvature, just above the pylorus.

Microscopic Observations.—Section of the ulcer showed the mucosa to end abruptly and the submucosa to be thickened and edematous for some distance on each side. The ulcer extended perpendicularly through the mucosa; its walls were infiltrated, and its base was acutely inflamed. Considerable autolysis was present at the base and involved the peritoneal surface as well. The peritoneum was covered with an acute fibrinopurulent exudate. The rest of the gastrointestinal tract was autolyzed but otherwise normal except for diffuse peritonitis. The renal tubules were degenerated and contained granular and hyaline casts. Many glomeruli contained granular exudate within the capsular space. Small infarctions with glomerular degeneration and lymphocytic infiltration were seen.

Dog 4.—A collie weighing 10.5 Kg. died on the seventeenth day of administration of cinchophen. Autopsy was not performed for several hours after death.

Gross Observations.—The peritoneal cavity contained gross blood. Autolysis was marked throughout the gastrointestinal tract; no definite gastric ulcers could be seen.

Microscopic Observations.—Autolysis was pronounced. However, a definite small ulcer was seen in the gastric mucosa, associated with diffuse subacute

gastritis. A small area of subacute inflammation of the submucosa was seen in the colon.

Dog 5.—A dog weighing 7 Kg. died after eight days of cinchophen treatment.

Gross Observations.—The dog was emaciated. Gross blood was observed in the intestinal tract. There were acute gastritis and enteritis.

Microscopic Observations.—There was diffuse acute superficial enteritis, with marked vascular congestion, necrosis and leukocytic infiltration. The gastric mucosa seemed to be within normal limits. There was congestion of the liver, lung and kidneys.

Dog 6.—A dog weighing 8 Kg. became acutely ill during the first week of administration of cinchophen. It seemed to recover, however, but its appetite

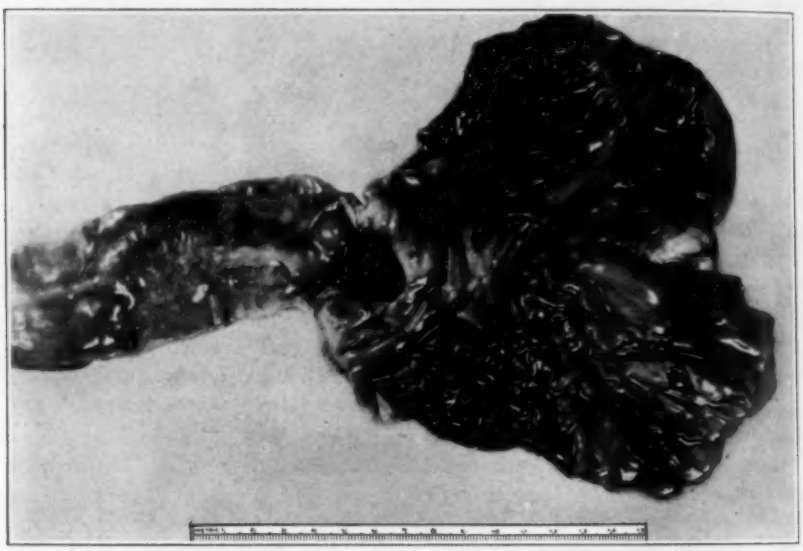

Fig. 3 (dog 6).—Photograph of the unfixed specimen, the stomach and a portion of the duodenum, showing a large perforated ulcer in the prepyloric area.

remained poor; it slowly lost weight, and it finally died, fifty-one days after starting the drug.

Gross Observations.—The dog was very emaciated. A large, deep ulcer on the lesser curvature, just above the pylorus, was seen to have eroded through the gastric wall. The liver, pancreas and gastrohepatic ligament were bound together in a mass of adhesions at the site of perforation.

Microscopic Observations.—The gastrointestinal tract was normal except for chronic indurated perforated gastric ulcer. There was acute local peritonitis. The spleen was loaded with phagocytes containing golden-brown pigment. The liver and kidneys were normal.

Dog 7.—A dog weighing 8.5 Kg. died on the thirty-second day of administration of cinchophen. Autopsy was unavoidably delayed for one day.

Gross Observations.—There were marked emaciation and acute diffuse peritonitis. A large perforated gastric ulcer on the lesser curvature, just above the pylorus, was present. Because of the state of decomposition no sections were made.

Dog 8.—A German shepherd dog weighing 22 Kg. was given cinchophen in doses of 150 mg. per kilogram of body weight for thirty days. The dog showed no toxic symptoms, remained lively and even gained weight. The dose was then increased to 200 mg. per kilogram for thirty days. There was no observable effect. The dog was playful, ate well and remained fat. Because the animal was desired for other purposes it was not killed for autopsy, but it was considered that this animal had failed to react to cinchophen with either the acute toxic response or the chronic ulcerative one.

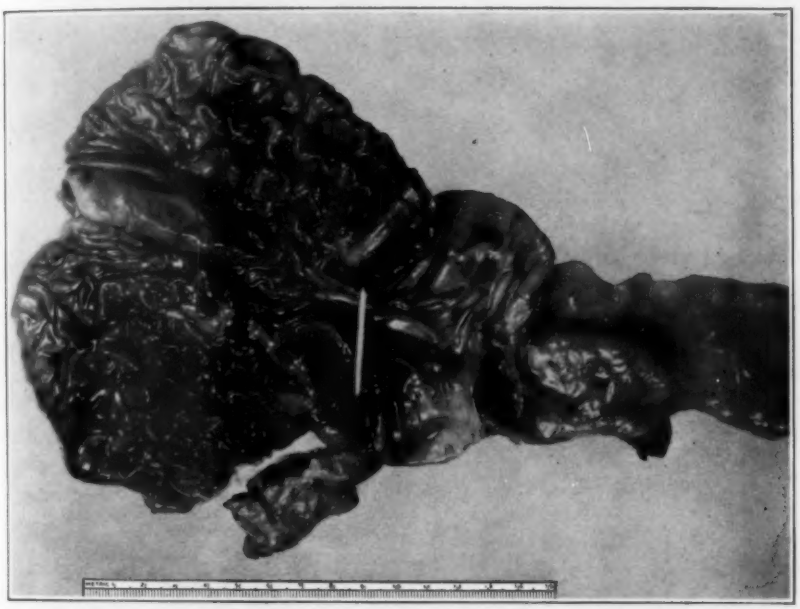

Fig. 4 (dog 9).—Photograph of the unfixed specimen, the stomach, gallbladder and duodenum, showing a punched-out ulcer just above the pylorus. The probe indicates the site of the cholecystogastrostomy stoma.

The surgically treated series comprised 5 animals. A summary of their protocols follows.

Dog 9.—A dog weighing 13 Kg. recovered without incident from the operation. Two weeks after operation administration of cinchophen was begun. The dog seemed well until about the fifteenth day, when it began to act ill and to lose weight. It went progressively downhill and died on the thirty-eighth day of administration of cinchophen.

Gross Observations.—The animal was emaciated. The anastomosis was well healed and patent. The common duct was ligated. There was a 2 cm. ulcer on the lesser curvature of the stomach, just above the pylorus.

Fig. 5 (dog 9).—Photograph of a cross section of the ulcer pictured in figure 4, showing perforation through the wall of the stomach to the liver. × 5.

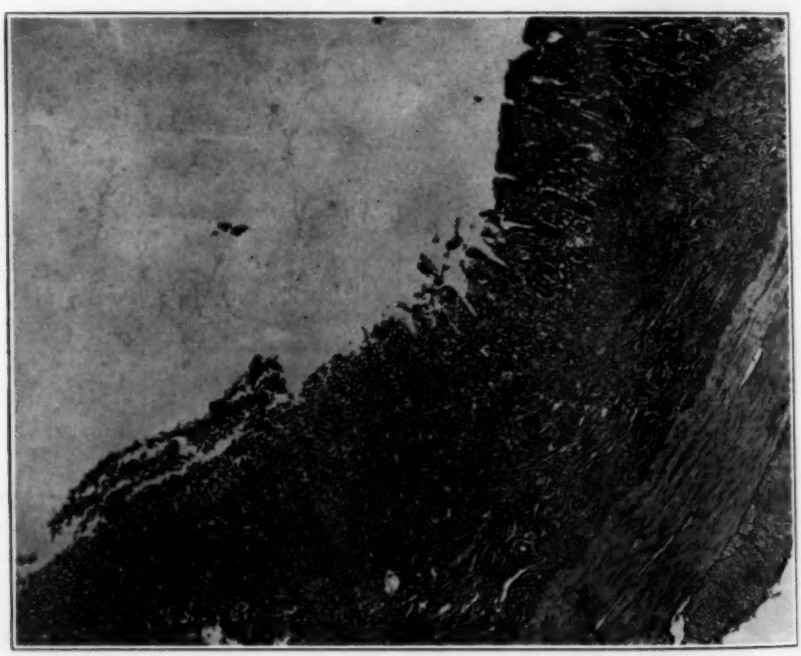

Fig. 6 (dog 9).—Photomicrograph of the edge of an ulcer in the ileum, showing destruction of the mucosa and an acute inflammation of the submucosa. × 41.

Microscopic Observations.—Ulcer: The ulcer extended entirely through the wall of the stomach, its base being formed by the adherent liver. Anastomosis: This was firmly healed by fibrosis. There was moderate chronic inflammation of the gallbladder. Small Bowel: There were areas of chronic ulceration extending into the submucosa. Kidneys: There were degeneration, edema precipitate in the capsular spaces and casts. Liver: This organ was normal.

Dog 10.—A German shepherd dog weighing 23 Kg. had a rapid, uneventful recovery from operation. Administration of cinchophen was begun on the ninth postoperative day. The dog was given 5 Gm. a day five days a week for sixty days without showing any toxic effect. It was then given 6 Gm. doses in capsules. It began to appear ill, lost weight and died on the one hundred and twenty-first day after administration of cinchophen was started.

Gross Observations.—The stomach contained no ulcers, but scattered throughout the jejunum and ileum were small necrotic ulcerations. The stoma was patent and the common duct ligated.

Microscopic Observations.—The stomach was normal except for much submucosal edema, and the anastomosis was well healed. The gallbladder was thickened with chronic inflammation. The small bowel showed areas of ulceration where the mucosa was destroyed, the muscularis mucosae lost and the submucosa thickened and inflamed. Some of the liver cells showed degenerative changes. The kidneys were normal.

Dog 11.—A dog weighing 5 Kg. recovered rapidly from the operation. Administration of cinchophen was begun on the thirteenth postoperative day. The dog soon appeared ill, lost weight and passed tarry stools; it died on the thirteenth day of administration of cinchophen.

Gross Observations.—There was emaciation. The stomach appeared normal and the stoma patent; the common duct had been severed. The small bowel contained multiple deep red erosions and ulcerations, and there was gross blood in the intestinal contents.

Microscopic Observations.—The stomach, liver and kidneys were normal. The stoma was well healed. The gallbladder showed subacute inflammation. The small bowel revealed multiple hemorrhagic erosions. Free hemorrhage occurred into the muscularis, into the submucosa and especially into the base of the mucosa, dissecting the glands off the basement membrane. Around the areas of hemorrhage there was an acute inflammatory reaction. Macrophages containing brown pigment could be seen in these areas. The large bowel contained ulcerations, a chronic inflammatory reaction of the submucosa forming the base. The spleen was crowded with macrophages filled with brown pigment.

Dog 12.—A dog weighing 10 Kg. made an uneventful recovery from operation. Administration of cinchophen was begun three weeks after operation. For two months it was administered in meat balls; there was not much evidence of toxicity. The dog then began to refuse the drug, and so it was administered in capsules. The animal soon began to appear somewhat thinner and less responsive but not acutely ill. Surgical exploration was done on the one hundred and eighteenth day of administration of cinchophen. No gastric lesion was found. On the sixth postoperative day the dog was eviscerated in a fight and died.

Gross Observations.—There was evisceration. Three major hepatic ducts fused to form the common duct, and the cystic duct came off one of the hepatic ducts. This hepatic duct had been ligated and severed. Part of the bile, therefore, had

entered the intestinal tract via the common duct and part via the cholecystogastrostomy opening. A 6 mm. ulcer was found just distal to the pylorus in the posterior duodenal wall.

Microscopic Observations.—The stomach contained small areas of subacute inflammation deep in the mucosa, involving the muscularis mucosae. The anastomosis was firmly knit and the mucosal surface entirely covered. The ulcer had a chronically inflamed base extending through the muscularis, with considerable fibrosis of the surrounding tissue. Recent acute inflammation, extending in under the edges and involving the adjacent muscularis, was seen. The liver showed subacute inflammation in the periportal areas, suggesting early cholangitis. The kidneys were normal.

Dog 13.—A dog weighing 7 Kg. seemed to lose its appetite after operation and loss of weight. However, it soon began to eat better, and it seemed well when administration of cinchophen was begun, four weeks after operation. It rapidly became sick, vomited, passed tarry stools and refused food. It died on the ninth day of treatment.

Gross Observations.—The dog was thin. A large, deep ulcer was located on the lesser curvature, just above the pylorus.

Microscopic Observations.—The ulcer showed an inflamed base extending all the way through the muscularis; the pancreas and the liver were adherent at this point. The edges were undermined and inflamed. The anastomosis was well healed; there was cholecystitis. The stomach was moderately congested; one small area of acute inflammation of the mucosa and submucosa was seen. Elsewhere it was normal. The liver showed acute cholangitis, but the parenchyma was not involved. The renal tubules showed slight cloudy swelling.

RESULTS

There was little observable difference in the reaction of the two series of animals to administration of cinchophen. All the animals in the group operated on and all but 1 of the control group showed gastrointestinal lesions which led to a fatal termination. Both groups likewise responded with a similar clinical reaction and a similar pathologic picture. From about the third to the eighth day there was a period of apparent acute toxemia—the animals lost their vigor, refused to eat, suffered nausea and vomiting and lost weight. Some of the animals died in this stage, and acute gastritis and enteritis were observed, together with cloudy swelling in the liver and kidneys. The lesions were diffuse, usually superficial, hemorrhagic and acutely inflamed. If the animal survived this period it seemed to become much less ill; energy and responsiveness returned, and it began to eat. Soon, however, it started to become thin. It tended to sit in a characteristic manner, the forefeet very close to the hindfeet and the abdomen drawn in as if the animal were suffering abdominal pain. Death for these animals was often rapid, following a perforation, or was preceded by a day or two of tarry stools indicating gross intestinal hemorrhage. Autopsy revealed a single

deep gastric or duodenal ulcer, multiple deep jejunal and ileal ulcers or, as in 1 animal, both types of lesions. The liver and kidneys tended to be normal. The accompanying table demonstrates this similarity of response of the two groups of animals.

COMMENT

The pathologic progress in both series of animals was entirely similar to that described by Bollman and his associates and by Simonds. Acute hemorrhagic and edematous gastritis with scattered areas of acute inflammation first appeared. These lesions then regressed, the mucosa tended to become normal except for one ulcer, which increased in size; the edges became undermined, and the ulcer extended deep into the muscularis. The lesion was almost invariably situated just above the pylorus, on the lesser curvature.

Several of the animals had similar ulcerations throughout the small bowel, a condition not emphasized in previous communications. In the acute phase these consisted of multiple scattered areas of hemorrhagic

Pathologic Observations

	Acute Gastritis and Enteritis	Chronic Peptic Ulcer	Ulcerative Enteritis	No Lesions
Control dogs	2	4	2	1
Surgically treated dogs	1	3	1	0

erosion and acute inflammation, with strands and masses of polymorphonuclear cells appearing in the mucosa. In the later stage the ulcerations became less numerous but much larger and deeper, being in some instances 2 or 3 cm. in diameter and extending halfway around the lumen of the intestine. The mucosa ended abruptly, and the adjacent submucosa was thickened and chronically inflamed. The base of the lesion was formed by thickened submucosa. The muscularis mucosae was destroyed, and the surface consisted of acute inflammatory tissue and necrotic debris. Rarely did these lesions extend into the muscularis itself, and, while hemorrhage from them was commonly observed, they were never seen to have perforated. The edges of such lesions are to be seen in figures 2 and 6. Whatever is the mode of action of cinchophen in causing gastrointestinal ulcerations, it seems apparent that it exerts its toxic effect throughout the length of the bowel.

My material also confirms the finding of others that there is no chronic or severe damage to the liver despite the massive and prolonged administration of cinchophen. Some cloudy swelling is noted in the acute toxic phase, but this tends to clear up. The only animal showing definite change in the liver was the dog who survived five months after

operation. This was subacute cholangitis, a lesion which has been found by many workers to appear almost invariably in dogs after cholecystogastrostomy. This subject has been reviewed by Gentile.[39]

The presence of a brownish pigment noted microscopically in several of the animals is of interest. It was seen in 1 case in the ulcerated areas in the stomach, in 2 in macrophages in the spleen and in 1 in the kidneys. It did not take an iron stain. The relation of this to the mode of action of cinchophen is not clear, but that there is a relation seems highly probable.

SUMMARY AND CONCLUSIONS

Two series of animals were fed old cinchophen five days a week. On one group, of 5 dogs, previous cholecystogastrostomy with ligation of the common duct was performed; the other group, of 8 dogs, served as controls.

No significant difference in the incidence of gastrointestinal ulcerations was noted in the two groups. All the animals of the surgically treated group and all but 1 of the control group died of intestinal lesions.

The presence of bile in the stomach is not adequate to protect that organ from the cinchophen-induced ulcer.

A hitherto unemphasized ulcerative enteritis occurring in a good percentage of both groups is described.

Cinchophen appears to be toxic to the mucosa of the entire intestinal tract.

Dr. W. C. Black furnished helpful criticisms and guidance throughout the work described.

39. Gentile, A.: Cholecystogastrostomy and Hepatitis, Arch. Surg. **30**:449 (March) 1935.

METABOLISM OF VITAMIN K AND ROLE OF THE LIVER IN PRODUCTION OF PROTHROMBIN IN ANIMALS

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The hemorrhagic tendency associated with obstructive jaundice, with prolonged biliary fistula and with certain types of hepatic damage has been a well recognized clinical entity for many years. However, elucidation of the underlying cause of the bleeding has been accomplished only recently. There have been many experimental studies of the various components of the blood which play a role in the process of coagulation, and until lately the cause of the clotting defect had not been found. Moss [1] in 1933 demonstrated that the concentration of plasma fibrinogen is normal in dogs with obstructive jaundice. Carr and Foote [2] in 1934 confirmed the results of Moss and showed that massive parenchymatous hemorrhage occurred in dogs with obstructive jaundice if life was prolonged to fifteen weeks.

In 1935 and 1936 Hawkins and Whipple [3] and Hawkins and Brinkhous [4] demonstrated the hemorrhagic tendency in dogs with biliary fistulas and showed that the bleeding was due to a deficiency of plasma prothrombin. The relation of vitamin K and the level of plasma pro-

This study was carried out under a grant from the John and Mary R. Markle Foundation.

From the Department of Surgery and Department of Pathology of the New York Hospital and Cornell University Medical College.

1. Moss, W.: Experimental Obstructive Jaundice: Its Effect on Fibrinogen and Coagulation of the Blood, Arch. Surg. **26**:1-19 (Jan.) 1933.

2. Carr, J. L., and Foote, F. S.: Progressive Obstructive Jaundice: Changes in Certain Elements of Blood and Their Relation to Coagulation, Arch. Surg. **29**:277-296 (Aug.) 1934.

3. Hawkins, W. B., and Whipple, G. H.: Bile Fistulas and Related Abnormalities: Bleeding, Osteoporosis, Cholelithiasis and Duodenal Ulcers, J. Exper. Med. **62**:599-620 (Oct.) 1935.

4. Hawkins, W. B., and Brinkhous, K. M.: Prothrombin Deficiency the Cause of Bleeding in Bile Fistula Dogs, J. Exper. Med. **63**:795-801 (June) 1936.

thrombin in dogs with biliary fistulas was determined by Smith, Warner, Brinkhous and Seegers [5] in 1938.

In 1937 Smith, Warner and Brinkhous [6] showed the intimate relation between plasma prothrombin and hepatic function by damaging the livers of dogs with chloroform. In their experiments the level of plasma prothrombin fell rapidly to 5 to 10 per cent of normal within twenty-four hours in cases of acute poisoning, and six to seven days elapsed before the return to normal was complete. Warner [7] performed partial hepatectomy in rats and was able to bring about a fall in the plasma prothrombin to 30 to 40 per cent of normal.

The experimental work on which the present paper is based is the study of the role of vitamin K and the liver in the formation of plasma prothrombin in the dog.

METHODS

Normal mongrel dogs weighing between 25 and 40 pounds (11.3 and 18.1 Kg.) were used, and obstructive jaundice was produced in certain of them by division of the common bile duct between ligatures. In some of these animals a cholecystectomy was also performed. Biliary fistulas were established in other dogs by the technic of Kapsinow, Engle and Harvey [8] by means of cholecystonephrostomy after ligation of the common duct. Total hepatectomy was performed by the methods of Mann [9] and of Markowitz, Yater and Burrows.[10] The technic of Warner, Brinkhous and Smith [11] was used in all determinations of the value for plasma prothrombin, and the vitamin K content of the livers was assayed by the curative method.

The diet of all the animals was carefully regulated, since Bollman and Mann [12] have demonstrated the importance of diet in any experimental study of the func-

5. Smith, H. P.; Warner, E. D.; Brinkhous, K. M., and Seegers, W. H.: Bleeding Tendency and Prothrombin Deficiency in Biliary Fistula Dogs: Effect of Feeding Bile and Vitamin K, J. Exper. Med. **67**:911-920 (June) 1938.

6. Smith, H. P.; Warner, E. D., and Brinkhous, K. M.: Prothrombin Deficiency and the Bleeding Tendency in Liver Injury (Chloroform Intoxication), J. Exper. Med. **66**:801-811 (Dec.) 1937.

7. Warner, E. D.: Plasma Prothrombin: Effect of Partial Hepatectomy, J. Exper. Med. **68**:831-835 (Dec.) 1938.

8. Kapsinow, R.; Engle, L. P., and Harvey, S. C.: Intra-Abdominal Biliary Exclusion from the Intestine; Cholecystnephrostomy, a New Method, Surg., Gynec. & Obst. **39**:62-65 (July) 1924.

9. Mann, F. C.: Studies in the Physiology of the Liver: I. Technic and General Effects of Removal, Am. J. M. Sc. **161**:37-42 (Jan.) 1921.

10. Markowitz, J.; Yater, W. M., and Burrows, W. H.: A Simple One-Stage Technic for Hepatectomy in the Dog, with Some Remarks on the Clinical Symptomatology of Terminal Hepatic Insufficiency, J. Lab. & Clin. Med. **18**:1271-1278 (Sept.) 1933.

11. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, Am. J. Physiol. **114**:667-675 (Feb.) 1936.

12. Bollman, J. L., and Mann, F. C.: The Physiology of the Impaired Liver, Ergebn. d. Physiol. **38**:445-492, 1936.

tion of the liver. A high carbohydrate, low fat, meat-free diet not only is of value in maintaining the health of dogs with hepatic damage but is effective in prolonging the life of animals with obstructive jaundice. The composition of the diet employed in all experiments was as follows:

Diet D-3

Food	Amount
Milk	500 cc.
Bread	4 slices
Karo	100 cc.
Tomato juice	30 cc.
Cod liver oil	4 cc.
Brewers' yeast	2 Gm.
Iron and ammonium citrates (50% solution)	4 cc. to each quart of tomato juice

This diet contains 32 Gm. of protein, 5 Gm. of fat and 184 Gm. of carbohydrate and has an approximate total caloric value of 909 calories. To illustrate the effectiveness of this diet in prolonging the lives of dogs with obstructive jaundice, two groups of animals are compared, one of which was fed a stock kennel food called diet D-1 while the other was fed the special diet D-3.

	Number of Dogs	Average Number of Days
Diet D-1	4	47
Diet D-3	5	75

OBSTRUCTIVE JAUNDICE

In 1934, Carr and Foote [2] produced in dogs the hemorrhagic tendency associated with obstructive jaundice. Their animals lived approximately fifteen weeks, and death was due to massive hemorrhage in 3 experiments and to hepatic insufficiency associated with cirrhosis in 2 others. They noted in the later stages of the experiments that, although the clotting time did not become prolonged, the clot was defective. It was bulky and fragile and failed to retract satisfactorily. The level of plasma fibrinogen showed no change during the experiment, thereby confirming the work of Moss,[1] who, in 1933, had failed to observe any change in this substance in dogs with biliary obstruction.

That the hemorrhagic tendency associated with obstructive jaundice in dogs is the result of a plasma prothrombin deficiency is evident in chart 1. After ligation and division of the common bile duct, the plasma prothrombin fell progressively to 15 per cent of normal in one hundred and five days. The death of the animal on the one hundred and eighteenth day was due to perforation of a duodenal ulcer and peritonitis.

In a group of 8 dogs in which obstructive jaundice was produced and which lived sixty-five days or more after operation, 3 exhibited parenchymatous hemorrhage at autopsy. For 2 of these 3 dogs the value for plasma prothrombin was below 20 per cent of normal, while for the third it was 30 per cent of normal.

All 8 animals showed reduced levels of plasma prothrombin, and at autopsy the livers were observed to be small, firm, dark green and mottled. On section the liver revealed white strands of fibrous tissue. Microscopically the picture was one of obstructive biliary cirrhosis, with a moderate amount of connective tissue bridging the portal spaces and infiltration with lymphocytic and a few mononuclear cells. Centrally, the biliary canaliculi contained plugs of inspissated bile. A characteristic observation in all but 2 animals was one or more duodenal ulcers, and in 2 instances perforation of the ulcer was directly responsible for the animal's death. In no dog was any bile found in the intestinal tract.

It seems evident from these experiments on the dog that the fall in plasma prothrombin associated with obstructive jaundice may be due to one or two factors or to their combination. In the first place, owing to ligation and division of the common ducts, bile cannot reach the intestinal tract, and presumably absorption of fat-soluble vitamins, such as vitamin K, is defective. Prothrombin formation is thereby interfered

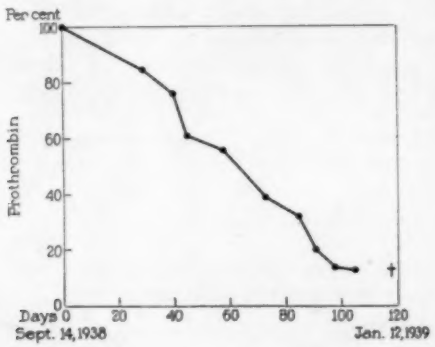

Chart 1.—Effect of ligation of the common bile duct on the level of plasma prothrombin.

with as the available stores of vitamin K are exhausted. Secondly, obstructive jaundice produces a conspicuous change in the liver, the later stage of which is represented by obstructive biliary cirrhosis, and hepatic functions—among them the production of prothrombin—suffer concomitantly with the morphologic changes in the liver.

BILIARY FISTULA

In order to eliminate the factor of obstructive cirrhosis, dogs were subjected to cholecystonephrostomy and division and ligation of the common bile duct by the method described by Kapsinow, Engle and Harvey. In 1935, Hawkins and Whipple [3] reported a variety of abnormalities which followed the establishment of biliary fistulas in dogs by this method, and among the changes noted purpura and spontaneous bleeding were conspicuous. Three to four months elapsed before hemorrhages were observed, and these investigators stated the belief that a

deficiency in plasma prothrombin was the underlying cause for the hemorrhage. In the next year Hawkins and Brinkhous [4] demonstrated the deficiency in prothrombin as the cause of the hemorrhagic tendency associated with biliary fistulas of prolonged duration and found that the feeding of whole bile both prevented and cured the condition.

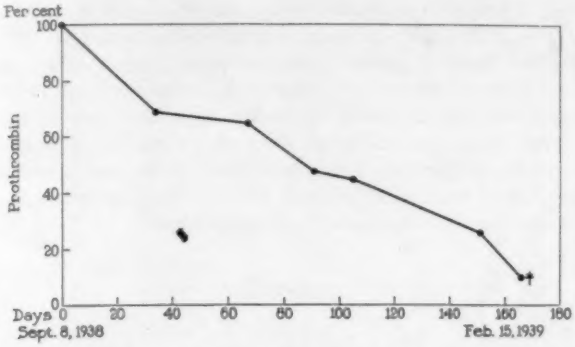

Chart 2.—Effect of an internal biliary fistula on the level of plasma prothrombin.

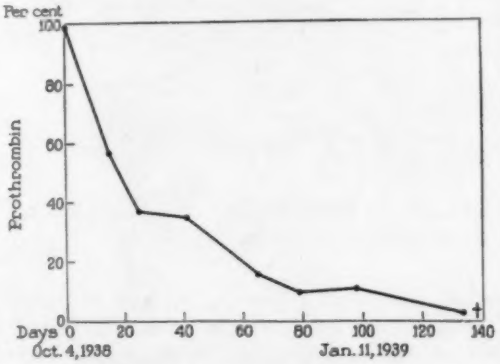

Chart 3.—Effect of feeding bile salts, 1 Gm. four times a day, to a dog with an internal biliary fistula.

Smith, Warner, Brinkhous and Seegers,[5] extending this work, observed that feeding bile salts alone was only partially effective in raising the plasma prothrombin. They found that whole bile was more effective than bile salts in elevating the level of plasma prothrombin but that administration of concentrated vitamin K in the presence of bile or bile salts brought about a rapid increase in the plasma prothrombin. They observed that viosterol was without effect.

An example of the characteristic fall in plasma prothrombin following the exclusion of bile from the intestinal tract but without hepatic damage can be seen

in chart 2. This animal was killed on the one hundred and sixty-fifth postoperative day while in a state of excellent health. That bile salts alone are not adequate to maintain the prothrombin level of the blood in the absence of excess vitamin K in the diet is demonstrated in chart 3. The animal represented had a biliary fistula for one hundred and thirty-five days and died as a result of a massive gastrointestinal hemorrhage with a plasma prothrombin level of only 5 per cent of normal. Autopsy demonstrated that the bleeding was parenchymatous.

Administration of bile salts with adequate intake of vitamin K, however, brings about a prompt rise of the level of plasma prothrombin (chart 4). The animal represented had a low level of plasma prothrombin as a result of a long-standing biliary fistula, and when 14,000 units of vitamin K (klotogen) and 14 Gm. of bile salts (bilron) were fed over a period of twelve days, the level of plasma prothrombin rose from 10 per cent to 70 per cent of normal. It is worthy of note that when the vitamin K therapy was discontinued there was a prompt fall in plasma prothrombin to a level of 20 per cent in eight days, indicating that storage of the vitamin in the liver had apparently not taken place.

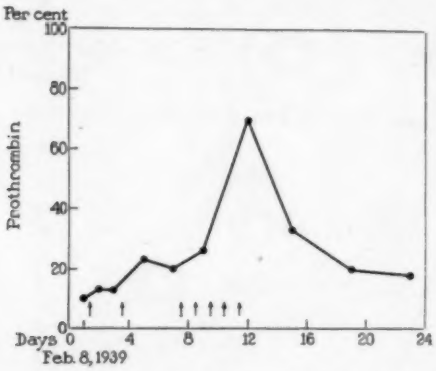

Chart 4.—Effect of feeding vitamin K (2,000 units) and bile salts (2 Gm.) to a deficient dog with an internal biliary fistula.

In order to investigate the relation between the level of plasma prothrombin and the amount of vitamin K in the liver, the vitamin K content of the livers of the aforementioned 14 dogs was assayed. In all, 7 dogs were subjected to ligation and division of the common bile duct; 5 dogs had biliary fistulas, and 2 animals (not operated on) were kept on the same diet as the operative groups for a similar length of time, approximately one hundred days. The liver of each animal was removed at autopsy after the dog had either been killed or died, and was dried by the cryochem process. The dried liver was then assayed for the curative value in vitamin K–deficient chicks. Chart 5 shows a spot graph of the results in which the terminal value for plasma prothrombin of the dog is plotted against the Howell prothrombin time of the treated chicks.

The normal liver evidently contains sufficient vitamin K so that the prothrombin time of the chicks to which it is fed is from six to ten minutes by the curative method of assay. Livers devoid of vitamin K are indicated by the chick's prothrombin time of thirty minutes. It is clear from the chart that there is a linear relation between the level of the plasma prothrombin and the vitamin K content of the liver. This is evidence that the value for plasma prothrombin falls

concomitantly with the depletion of the store of vitamin K in the liver, and that the fall is not delayed until the store is exhausted.

In order to observe the effect of instillation of vitamin K and bile salts directly into the duodenum at laparotomy, a dog with a biliary fistula which had a plasma prothrombin concentration of 18 per cent was operated on, and 10,000 units of

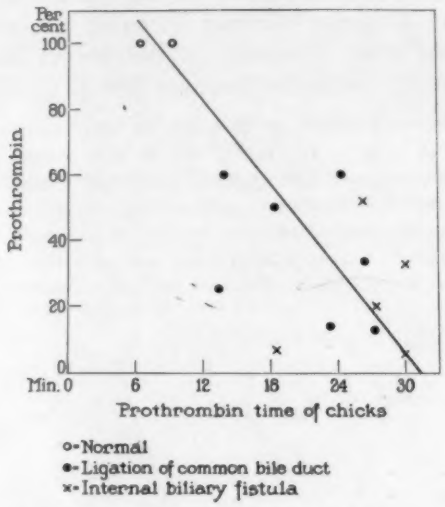

Chart 5.—Vitamin K content of the liver in relation to plasma prothrombin.

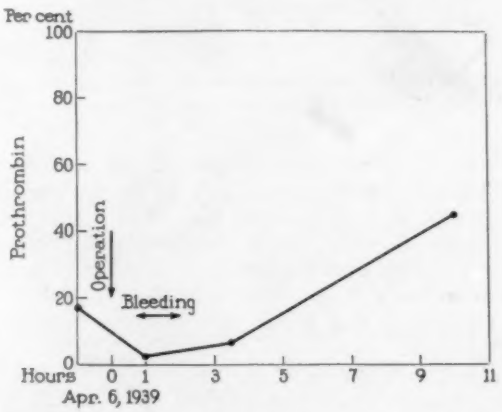

Chart 6.—Effect of instillation into the duodenum at laparotomy of 10,000 units of vitamin K and 2 Gm. of bile salts in a dog with an internal biliary fistula.

vitamin K (klotogen) and 2 Gm. of bile salts (bilron) were instilled directly into the duodenum. The level of plasma prothrombin fell immediately postoperatively, and associated with this there was hemorrhage from the wound. Within ten hours of the operation the level of plasma prothrombin had risen to 45 per cent of normal (chart 6). Twenty-one hours after the instillation of vitamin K the value was 65 per cent of normal. Three days later it had again fallen to less than 5 per cent of normal.

ROLE OF LIVER IN SYNTHESIS OF PROTHROMBIN

Smith, Warner and Brinkhous,[6] using chloroform as the hepatotoxin, observed a precipitous fall in plasma prothrombin to less than 10 per cent of normal within twenty-four hours of the chloroform anesthesia, and the return to normal was not complete until six days had elapsed. With the foregoing evidence in mind, we have studied the plasma prothrombin after a variety of injuries to the liver: (1) mechanical trauma, (2) partial hepatectomy and (3) total hepatectomy.

The effect of mechanical trauma to the liver on the plasma prothrombin was investigated by one of us (J. W. L.[13]), and it was found that after gentle massage of the liver for twenty-five minutes a precipitous fall occurred in the level of plasma prothrombin to 75 per cent of normal and that the return to normal was not complete until sometime between the fourth and the seventh postoperative day (chart 7). Simple laparotomy and operations of the magnitude of a gastroenterostomy were without effect on the plasma prothrombin.

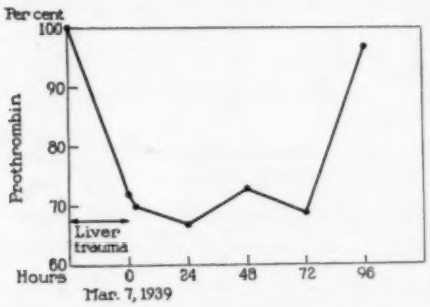

Chart 7.—Effect of mechanical trauma to the liver on the level of plasma prothrombin.

Partial hepatectomy in which approximately 25 per cent of the liver was removed in 1 dog was followed by a progressive fall in the level of plasma prothrombin to 60 per cent of normal within forty-eight hours and a return to normal after seven days. A second animal showed a similar fall in the level of plasma prothrombin following partial hepatectomy but died of bronchopneumonia on the third postoperative day.

Andrus, Lord and Moore [14] and Warren and Rhoads [15] independently performed total hepatectomy in dogs and found that the plasma prothrombin fell progressively to low levels. The former investigators

13. Lord, J. W., Jr.: The Effect of Trauma to the Liver on the Plasma Prothrombin: An Experimental Study, Surgery **6**:896-898 (Dec.) 1939.

14. Andrus, W. DeW.; Lord, J. W., Jr., and Moore, R. A.: The Effect of Hepatectomy on the Plasma Prothrombin and the Utilization of Vitamin K, Surgery **6**:899-900 (Dec.) 1939.

15. Warren, R., and Rhoads, J. E.: The Hepatic Origin of the Plasma-Prothrombin Observations After Total Hepatectomy in the Dog, Am. J. M. Sc. **198**:193-197 (Aug.) 1939.

found that the concentration fell to less than 20 per cent of normal in ten hours and to 5 per cent of normal in 2 dogs that lived longer than ten hours (chart 8), and that instillation of 10,000 units of vitamin K and 2 Gm. of bile salts into the duodenum at the end of the operation failed to alter the typical curve observed in the hepatectomized animals without such instillation.

It is evident that, regardless of the mode of injury to the liver, such injury is reflected in a prompt fall in the concentration of plasma prothrombin.

COMMENT

In many respects there is some similarity between the underlying mechanism responsible for the bleeding tendency due to lowered concentrations of plasma prothrombin and that producing anemia of the

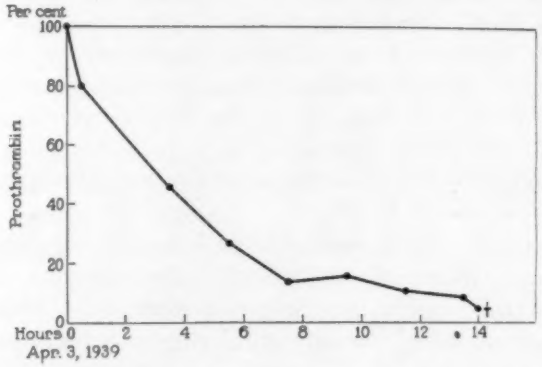

Chart 8.—Effect of total hepatectomy on the level of plasma prothrombin.

addisonian type. In the latter the extrinsic factor in the diet is comparable to vitamin K itself, while the intrinsic gastric factor may be compared to the bile salts needed for absorption of vitamin K. In the young chicken, lowered levels of plasma prothrombin have been occasioned by diets deficient in vitamin K. In the dog, absence of bile salts in the intestinal tract is responsible for failure of absorption of vitamin K. Whether there is an actual chemical reaction between this vitamin and bile salts or whether the bile salts act simply as a carrier of the vitamin K across the intestinal epithelium is as yet unsettled. That the latter view is probably correct is substantiated by the prompt and significant rise of 30 per cent in the plasma prothrombin within forty-eight hours in dogs given intramuscular injections of crystalline vitamin K principle, 2-methyl-1, 4-naphthoquinone in oil.[16] Doses as small as 1 mg.

16. Andrus, W. DeW., and Lord, J. W., Jr.: The Correction of Prothrombin Deficiency by Means of 2-Methyl-1, 4-Naphthoquinone Injected Intramuscularly, J. A. M. A. **114**:1336-1337 (April 6) 1940.

are effective. The lack of the intrinsic factor in the stomach in the presence of pernicious anemia and the defective absorption of the combined factor in the presence of sprue both act to deprive the liver of the antianemic factor. Likewise, the absence of bile salts in the intestine in the presence of obstructive jaundice or biliary fistula results in failure of absorption of vitamin K and therefore deprives the liver of that necessary element in the formation of plasma prothrombin.

That the liver forms plasma prothrombin is established beyond a reasonable doubt by the experimental evidence concerning the dog just mentioned. Total or partial removal of the liver and mechanical or chemical trauma to the liver are reflected by prompt changes in the concentration of plasma prothrombin. In the dog with total extirpation of the liver the plasma prothrombin falls to extremely low levels (less than 10 per cent of normal), and the hemorrhagic diathesis becomes manifest in as short a period as fourteen hours after the operation. Similarly, in the presence of chronic hepatic insufficiency as seen in cases of cirrhosis of the liver, in human beings, a macrocytic anemia is a prominent feature of that disease. As the liver stores the antianemic principle, it likewise stores vitamin K in dogs. This storage is evidenced by the protective action of the dried livers of dogs when assayed in vitamin K–deficient chicks.

In résumé, into the final formation of plasma prothrombin there enter an extrinsic factor, vitamin K, an intrinsic factor, bile salts, an absorptive mechanism, the intestinal epithelium, and the liver, which, in the case of plasma prothrombin, not only stores vitamin K but elaborates the plasma prothrombin.

The fate of plasma prothrombin after its formation in the liver and release into the circulating blood has been the subject of some recent experimental work.[17] Certain studies point to the lungs as the site of disappearance of plasma prothrombin. Samples of circulating blood taken simultaneously from the arterial and the venous supply of various organs in the dog revealed no significant variation in the level of plasma prothrombin, with the one exception of blood circulating to and from the lungs. In 17 of 20 experiments (85 per cent) plasma prothrombin in the samples of blood taken from the left ventricle averaged 10.6 per cent less than in samples from the right ventricle.

A possible explanation of this role of the lung in the loss of plasma prothrombin is thought to be the production of blood platelets in this organ, as demonstrated by Howell and Donahue.[18] Platelets, as they

17. Andrus, W. DeW.; Lord, J. W., Jr., and Kauer, J. T.: Studies on the Fate of Plasma Prothrombin, Science **91**:48-50 (Jan. 12) 1940.

18. Howell, W. H., and Donahue, D. D.: The Production of Blood Platelets in the Lungs, J. Exper. Med. **65**:177-203 (Feb.) 1937.

undergo disintegration, initiate the first stage of the clotting process by releasing thromboplastin, which, in the presence of calcium, changes prothrombin to thrombin.

SUMMARY AND CONCLUSIONS

A brief historical résumé of some of the experimental evidence concerning the relation between the hemorrhagic diathesis, plasma prothrombin and vitamin K is presented.

The protective effect on the liver of a carefully selected diet is demonstrated.

Bile must reach the intestinal tract for the proper absorption of the fat-soluble vitamin K. The essential substance in bile is the bile salts.

In dogs with obstructive jaundice or biliary fistula, bile salts alone when fed by mouth in the absence of added vitamin K do not suffice to prevent a fall in the level of plasma prothrombin.

Vitamin K after absorption is stored in the liver. Partial loss of the stores of vitamin K in the liver is reflected in a linear manner by a fall in the level of plasma prothrombin.

The liver is the site of formation of plasma prothrombin. A healthy, normally functioning liver is required for the maintenance of a normal level of plasma prothrombin.

A comparison has been made between the factors whose derangement results in pernicious anemia and the vitamin K–plasma prothrombin relation. That these two entities are decidedly similar physiologically and anatomically is noted.

Prothrombin is continuously disappearing from the circulating blood, and experiments point to the lung as the site of this loss.

When plasma prothrombin falls to low levels because of inadequate absorption, hepatic damage or both, the hemorrhagic tendency becomes manifest. The critical level of the plasma prothrombin is approximately 20 per cent of normal by the method used in these studies.

CLINICAL INVESTIGATIONS OF SOME FACTORS CAUSING PROTHROMBIN DEFICIENCIES

SIGNIFICANCE OF THE LIVER IN THEIR PRODUCTION AND CORRECTION

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The hemorrhagic tendency sometimes seen in patients with obstructive jaundice has been the subject of a great deal of clinical and experimental investigation since Smith [1] remarked on it nearly fifty years ago. This has now culminated in discovery of the underlying deficiency and of measures by which it can promptly be corrected in most cases. In the process of the investigations many bypaths have also been explored, and while in them the ultimate cause was not found, among the accumulated data facts were encountered which contributed to the final solution of the problem. The spectacular developments of the past few years are due in part at least to such facts and to theories developed over many years as one after another of the recognized clotting elements of the blood was considered as possibly involved and then dismissed.

A deficiency of calcium was long held to be of importance,[2] and as finer methods became available for studying the various fractions of this element in the blood, these too were studied,[3] but without consistent results. Changes in the fibrinogen content of the blood were also considered, but such alterations as were demonstrable in cases of obstructive jaundice were not consistent and tended to be on the side of increase rather than of decrease in this component.[4]

This study was carried out under a grant from the John and Mary R. Markle Foundation.

From the Department of Surgery of the New York Hospital and Cornell University Medical College.

1. Smith, G.: Abdominal Surgery, Philadelphia, P. Blakiston's Son & Co., 1891, p. 610.

2. King, J. H., and Stewart, H. A.: The Effect of the Injection of Bile on the Circulation, J. Exper. Med. **11**:673, 1909. Walters, W.: Pre-Operative Preparation of Patients with Obstructive Jaundice, Surg., Gynec. & Obst. **33**:651, 1921. Lee, R. I., and Vincent, B.: The Relation of Calcium to the Delayed Coagulation of Blood in Obstructive Jaundice, Arch. Int. Med. **16**:59 (July) 1915.

3. Gunther, L., and Greenberg, D. M.: Diffusible Calcium and Protein of Blood Serum in Jaundice, Arch. Int. Med. **45**:983 (June) 1930.

These fibrinogen studies were the first of a number in which deviations from the normal values of several constituents of blood, such as dextrose,[5] cysteine and the related mercaptans [6] and the lipid amino nitrogen compounds,[7] were described as accompanying obstructive jaundice and were considered as possibly responsible for the bleeding tendency. Subsequent work, however, indicates that they are better explained as results of damage to the liver associated with the cause of the jaundice or due to obstructive cirrhosis, being thus concomitants rather than causes of the hemorrhagic tendency.

Clinical and laboratory tests designed to detect abnormalities of the clotting mechanism were improved and demonstrated more conclusively qualitative defects, as expressed in prolonged bleeding time in the presence of stasis [8] and poor retractility of the clot.[9] Methods later appeared for more accurate estimation of the prothrombin content of the plasma,[10] which finally led to the discovery that the level of this component of the clotting mechanism may be depressed when bile is absent from the intestinal tract and that it is consistently and markedly lowered in subjects who show the bleeding tendency either in cases of obstructive jaundice [11] or in cases of biliary fistula.[12]

4. Linton, R. R.: Relation of Blood Fibrin to Haemorrhagic Diathesis of Obstructive Jaundice, Ann. Surg. **96**:394, 1932. Lewisohn, R.: Haematologic Studies as Basis for Determining Risk of Post-Operative Haemorrhage in Jaundice Patients, ibid. **94**:80, 1931. Moss, W.: Experimental Obstructive Jaundice: Its Effect on Fibrinogen and Coagulation of the Blood, Arch. Surg. **26**: 1 (Jan.) 1933.

5. Partos, A., and Švec, F.: Gesetzmässiger Zusammenhang zwischen Blutzuckergehalt und Blutgerinnungszeit, Arch. f. d. ges. Physiol. **218**:209, 1927. Cannon, W. B., and Gray, H.: Factors Affecting the Coagulation Time of Blood, Am. J. Physiol. **34**:232, 1914.

6. Carr, J. L., and Foote, F. S.: Progressive Obstructive Jaundice, Arch. Surg. **29**:277 (Aug.) 1934.

7. Andrus, W. DeW., and Moore, R. A.: Lipid Amino Nitrogen Content of the Blood in Diseases of the Liver and Biliary Tract, Arch. Surg. **39**:3 (July) 1939.

8. Ivy, A. C.; Shapiro, P. F., and Melnick, P.: The Bleeding Tendency in Jaundice, Surg., Gynec. & Obst. **60**:781, 1935.

9. Boyce, F. F., and McFetridge, E. M.: A Serum Volume Test for the Hemorrhagic Diathesis in Jaundice, J. Lab. & Clin. Med. **23**:202, 1937.

10. (*a*) Quick, A. J.; Stanley-Brown, M., and Bancroft, F. W.: A Study of the Coagulation Defect in Hemophilia and Jaundice, Am. J. M. Sc. **190**:501, 1935. (*b*) Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, Am. J. Physiol. **114**:667, 1936.

11. Bancroft, F. W.; Kugelmass, I. N., and Stanley-Brown, M.: Evaluation of Blood Clotting Factors in Surgical Diseases, Ann. Surg. **90**:161, 1929. Nygaard, K. K.: Coagulability of Blood Plasma: Remarks on Technic of Its Determination, Proc. Staff Meet., Mayo Clin. **9**:151, 1934. Lewisohn.[4b]

(Footnotes continued on next page)

The general effects of jaundice or of prolonged loss of bile through external biliary fistulas on appetite and nutrition had been recognized for many years, and as long ago as 1907 Halsted advised and in his own cases carried out the collection of bile from such fistulas and its administration to patients by means of a stomach tube—a practice since become common in many clinics. A renewed interest in the importance of the presence of bile in the intestinal tract was awakened when it was shown [13] that in its absence absorption of the fat-soluble vitamins D and A was interfered with.

The discovery of a new accessory food factor, the fat-soluble vitamin K,[14] lack of which caused hemorrhagic disease in chicks, and the demonstration [15] that restriction of this vitamin in the diet of chicks is associated with lowered levels of the prothrombin content of the plasma suggested that a similar situation might be responsible for the prothrombin deficiency associated with obstructive jaundice.

It was soon demonstrated that this was the case in rats when bile was absent from the intestinal tract in the presence of either obstructive jaundice or biliary fistula,[16] since, as with other fat-soluble vitamins (A and D), bile salts are essential for absorption from the intestine. The deficiency could be corrected by administration of vitamin K and bile salts. The similar deficiency in dogs has also been demonstrated [17] and corrected by the use of bile salts and alfalfa extracts.

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12. Hawkins, W. B., and Whipple, G. H.: Bile Fistulas and Related Abnormalities: Bleeding, Osteoporosis, Cholelithiasis and Duodenal Ulcers, J. Exper. Med. **62**:599, 1935. Hawkins, W. B., and Brinkhous, K. M.: Prothrombin Deficiency the Cause of Bleeding in Bile Fistula Dogs, ibid. **63**:759, 1936.

13. Greaves, J. D., and Schmidt, C. L. A.: Further Experiments on Role Played by Bile in Absorption of Vitamin D in Rat, Univ. California Publ., Physiol. **8**:43, 1934; On the Absorption and Utilization of Carotene and Vitamin A in Choledochocolonostomized Vitamin A Deficient Rats, Am. J. Physiol. **111**:492, 1935.

14. Dam, H.: Haemorrhages in Chicks Reared on Artificial Diets: New Deficiency Disease, Nature, London **133**:909, 1934. Almquist, H. J., and Stokstad, E. L. R.: Hemorrhagic Chick Disease of Dietary Origin, J. Biol. Chem. **116**:105, 1935. Dam, H.: Antihaemorrhagic Vitamin of Chick: Occurrence and Chemical Nature, Nature, London **135**:652, 1935.

15. Dam, H.; Schønheyder, F., and Tage-Hansen, E.: Studies on Mode of Action of Vitamin K, Biochem. J. **30**:1075, 1936.

16. Greaves, J. D., and Schmidt, C. L. A.: Nature of the Factor Concerned in Loss of Blood Coagulability of Bile Fistula Rats, Proc. Soc. Exper. Biol. & Med. **37**:43, 1937.

17. Smith, H. P.; Warner, E. D.; Brinkhous, K. M., and Seegers, W. H.: Bleeding Tendency and Prothrombin Deficiency in Biliary Fistula Dogs, J. Exper. Med. **67**:911, 1938. Lord, J. W., Jr.; Andrus, W. DeW., and Moore, R. A.: Metabolism of Vitamin K and Role of the Liver in Production of Prothrombin in Animals, Arch. Surg., this issue, p. 585.

Widespread clinical application of these findings has confirmed both the significance of vitamin K in restoration of the plasma prothrombin to a normal level and the importance of bile salts in influencing its absorption from the intestinal tract.[18] Various vitamin K extracts were used in the earlier series, many of them very crude as compared to the more recent compounds, but the results have been for the most part highly satisfactory.

We have followed the plasma prothrombin levels in two groups of cases of disease of the biliary tract and other conditions associated with deficiencies in this clotting component. In the first series 22 patients were found to have low prothrombin levels and were therefore treated with vitamin K (klotogen or cerophyl) and bile salts (bilron). By means of such therapy, plus transfusions for certain patients, we were able uniformly to bring about a cessation of hemorrhage when it was present at the time of admission or to prevent its subsequent occurrence, except in 1 patient with carcinoma involving the bile passages, who died from a massive hemorrhage from an ulcer on the posterior aspect of the duodenum which had eroded into the pancreaticoduodenal artery. In this patient the prothrombin level of the plasma had previously been low but had responded promptly to appropriate therapy and at the time of the hemorrhage was normal. Quite obviously the bleeding was unconnected with any prothrombin deficiency.

In the course of further work on the chemical composition of the vitamin it was finally isolated[19] in two forms, which were shown to be 1, 4-naphthoquinones. Almquist and Klose[20] showed that phthiocol (2-methyl, 3 hydroxy-1, 4-naphthoquinone) possesses some vitamin K activity, and, being readily available, this substance has been satisfactorily employed both orally and intravenously for the correction of prothrombin

18. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: Bleeding Tendency of Obstructive Jaundice: Prothrombin Deficiency and Dietary Factors, Proc. Soc. Exper. Biol. & Med. **37**:628, 1938. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: The Use of Vitamin K in Treatment of the Hemorrhagic Diathesis in Cases of Jaundice, Proc. Staff Meet., Mayo Clin. **13**:74, 1938; Further Observations on the Use of Vitamin K in the Prevention and Control of the Hemorrhagic Diathesis in Cases of Jaundice, ibid. **13**:753, 1938. Rhoads, J. E.: The Relation of Vitamin K to the Hemorrhagic Tendency in Obstructive Jaundice, with a Report on Cerophyl as a Source of Vitamin K, Surgery **5**:794, 1939. Stewart, J. D.; Rourke, G. M., and Allen, A. W.: Control of Postoperative Bleeding in Obstructive Jaundice, Tr. Am. S. A. **57**:258, 1939.

19. McKee, R. W.; Binkley, S. B.; MacCorquodale, D. W.; Thayer, S. A., and Doisy, E. A.: The Isolation of Vitamin K_1 and K_2, J. Am. Chem. Soc. **61**: 1295, 1939.

20. Almquist, H. J., and Klose, A. A.: The Anti-Hemorrhagic Activity of Pure Synthetic Phthiocol, J. Am. Chem. Soc. **61**:1611, 1939.

deficiencies.[21] The vitamin itself is believed to be 2-methyl-3, phytyl-1, 4-naphthoquinone,[22] and several other related compounds have been found to possess lesser degrees of vitamin K activity.

By far the most potent of all compounds so far investigated is synthetic 2-methyl-1, 4-naphthoquinone, which has been shown to be several hundred times as potent as phthiocol.[23] A recent study [24] indicates that its activity is as great as 30,000,000 Dam units per gram, so that it is effective in extremely minute doses. When it is given by mouth, bile salts are of course essential for its absorption from the gastrointestinal tract, and Rhoads and Fliegelman [25] have recently reported satisfactory response to its administration by this route in 10 cases.

In August 1939 we began to use this substance exclusively for the treatment of prothrombin deficiencies, and at first, while we were conducting a series of experiments on animals to determine its effect and possible toxicity when injected intramuscularly dissolved in oil, it was administered orally. When our studies had demonstrated its effectiveness and lack of toxicity by intramuscular injection, we turned to this route with good effect, and since October 1 we have employed it in 38 cases, with strikingly successful results in the absence of damage to the liver. Synthetic 2-methyl-1, 4-naphthoquinone is inexpensive, and intramuscular injection of this substance dissolved in corn oil is so simple and effective that we believe this to be the simplest method of administration in the treatment of prothrombin deficiencies. When it is given by injection, the presence of bile salts in the intestinal tract is not necessary for its absorption, and its effect is evident within a few hours. Moreover, the influence of a single injection on the concentration of plasma prothrombin may be prolonged, in many cases for at least a week. As in the case of other substances with vitamin K activity, however, it would appear from both experimental and clinical work that its effectiveness may be diminished or even abolished in the presence of severe damage to the liver.

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21. Smith, H. P.; Ziffren, S. E.; Owen, C. A., and Hoffman, G. R.: Clinical and Experimental Studies on Vitamin K, J. A. M. A. **113**:380 (July 29) 1939. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: Phthiocol: Its Therapeutic Effect in the Treatment of Hypoprothrombinemia Associated with Jaundice: Preliminary Report, Proc. Staff Meet., Mayo Clin. **14**:497, 1939.

22. MacCorquodale, D. W.; Binkley, S. B.; Thayer, S. A., and Doisy, E. A.: On the Constitution of Vitamin K, J. Am. Chem. Soc. **61**:1928, 1939.

23. Ansbacher, S., and Fernholz, E.: Simple Compounds with Vitamin K Activity, J. Am. Chem. Soc. **61**:1924, 1939.

24. Sjögren, B.: Die Vitamin K-Wirkung einiger Naphthochinone und Naphthochinonderivate, Ztschr. f. physiol. Chem. (nos. 3-5) **262**:1-3, 1939.

25. Rhoads, J. E., and Fliegelman, M. J.: The Use of 2-Methyl-1, 4-Naphthoquinone (A Synthetic Vitamin K Substitute) in Treatment of Prothrombin Deficiency in Patients, J. A. M. A. **114**:400 (Feb. 3) 1940.

In the preceding paper, covering animal experiments, certain points regarding the specificity of vitamin K, various aspects of its absorption and metabolism and its relation to the formation of prothrombin have been emphasized. Many of these points find confirmation in the following clinical reports. Thus chart 1 illustrates the course of a patient who was deeply jaundiced as a result of obstruction of the common duct due to carcinoma of the bile duct at a time when vitamin K therapy was not available.[26] Although bile salts were admistered and a number of transfusions given, it is evident that there was a definite vitamin K defi-

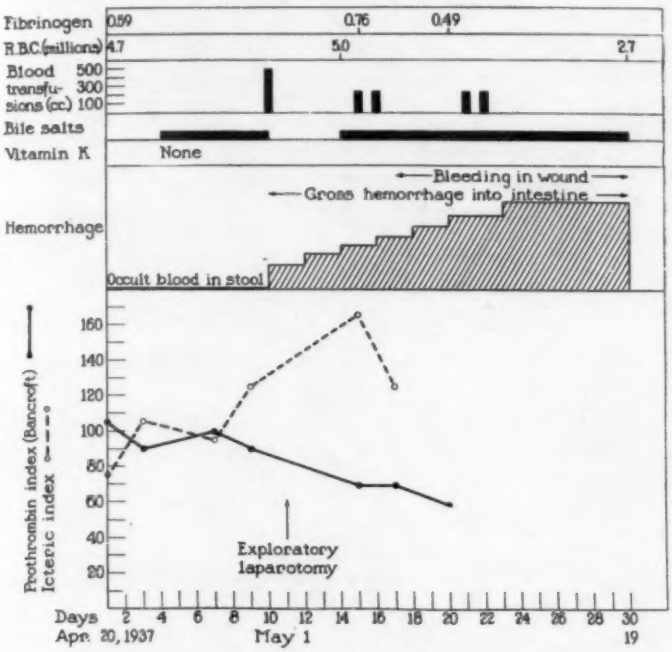

Chart 1.—Data in the case of a man aged 67. Autopsy revealed carcinoma of the bile duct, with complete obstruction and hemorrhage in the viscera.

ciency in this case, with consequent lowering of the level of plasma prothrombin and severe bleeding. Fortunately, only a relatively small proportion of patients with obstructive jaundice showed the bleeding tendency even in the days before the underlying cause was known, probably, as is now known, because there is a sufficient reserve of vitamin

26. The prothrombin curve in chart 1 is in terms of the prothrombin index, with which the critical bleeding level is 70. The prothrombin curves in all other figures are in terms of per cent of normal by the test of Warner, Brinkhous and Smith.[10b] In this the bleeding level is 20 to 25 per cent.

K in the liver to maintain the concentration of prothrombin above the critical bleeding level for some time before it is exhausted.

That vitamin K may fail to be absorbed even in the presence of bile salts is evident in the case the course of which is depicted in chart 2. This patient, with so-called nontropical sprue, was suffering from severe diarrhea, with the passage of frothy stools daily. Administration of bile salts and vitamin K in ordinarily adequate amounts failed completely to elevate the level of plasma prothrombin.

On the other hand, chart 3 illustrates the dramatic response to appropriate therapy in what would probably have been a fatal case prior to

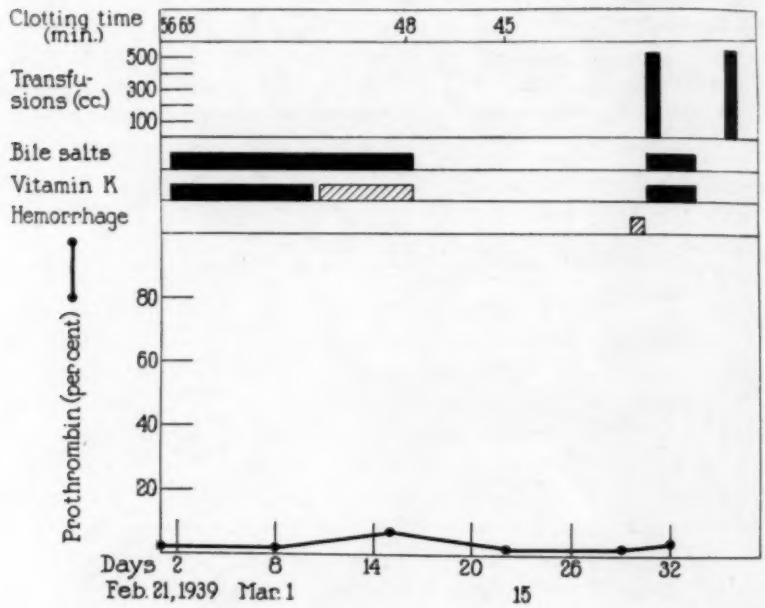

Chart 2.—Data in the case of a woman aged 41. The diagnosis was nontropical sprue.

recognition of the fundamental defect and of means of correcting it. The patient, who had suffered for eighteen months from cicatricial stenosis of the common duct, was bleeding from the intestinal tract at the time of admission. Transfusions were first administered both to restore the blood lost and as a means of supplying prothrombin directly, and at the same time adequate amounts of a vitamin K concentrate and bile salts were administered orally. The hemorrhage was promptly controlled, and the plasma prothrombin was elevated within a few days to the normal level. Such a response is to be expected unless some other factor, such as damage to the liver, interferes with the production of prothrombin.

The depressing effect of damage to the liver on the level of plasma prothrombin can be strikingly demonstrated in animals,[27] and, after complete hepatectomy at least, administration of even large doses of vitamin K fails to alter materially the curve of fall. Clinical observations of the failure of response to vitamin K therapy in the presence of damage to the liver are depicted in charts 4 and 5. The patient whose course is illustrated in chart 4 was a 50 year old woman who was

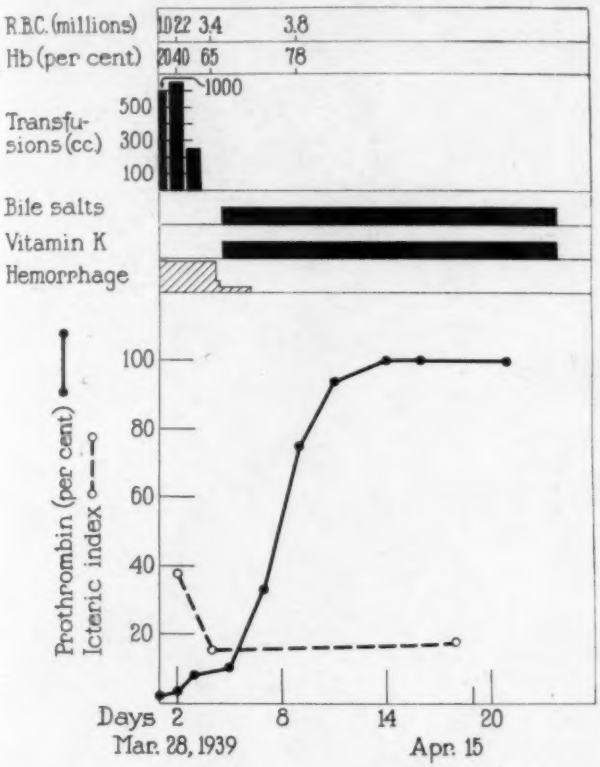

Chart 3.—Data in the case of a woman aged 47. The diagnosis was inflammatory stenosis of the common bile duct.

27. Smith, H. P.; Warner, E. D., and Brinkhous, K. M.: Prothrombin Deficiency and the Bleeding Tendency in Liver Injury (Chloroform Intoxication), J. Exper. Med. **66**:801, 1937. Warner, E. D.: Plasma Prothrombin: Effect of Partial Hepatectomy, ibid. **68**:831, 1938. Andrus, W. DeW.; Moore, R. A., and Lord, J. W., Jr.: The Effect of Hepatectomy, on the Plasma Prothrombin and the Utilization of Vitamin K, Surgery **6**:899, 1939. Lord, J. W., Jr.: The Effect of Trauma to the Liver on the Plasma Prothrombin, ibid. **6**:896, 1939. Warren, R., and Rhoads, J. E.: The Hepatic Origin of the Plasma Prothrombin Observation After Total Hepatectomy in the Dog, Am. J. M. Sc. **198**:193, 1939.

admitted to the hospital with a temperature of 40 C. She had suffered intermittently from symptoms of disease of the gallbladder for eighteen years and had been somewhat jaundiced for five weeks. Her condition was so precarious that she was treated conservatively with blood transfusions, clysis and administration of vitamin K and bile salts for four days and was then subjected to a cholecystostomy. At operation an inflammatory mass was found about the lower portion of the gallbladder and overlying the common duct. The value for plasma prothrombin, which was 25 per cent of normal on admission, rose promptly to normal after vitamin K and bile salts were administered, but after the eighth

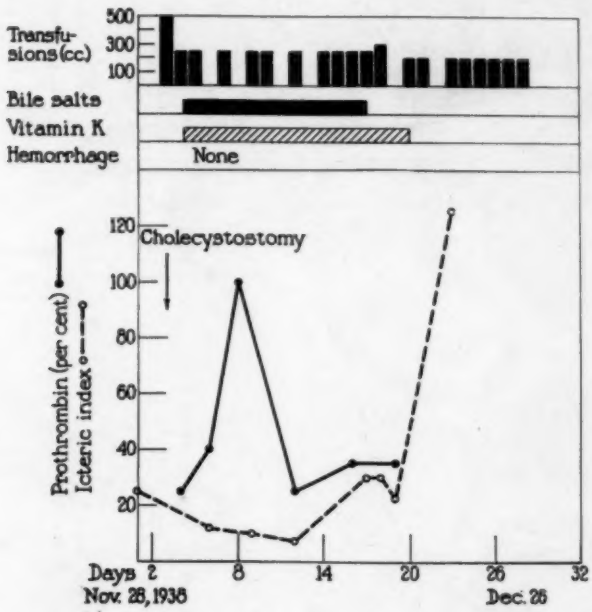

Chart 4.—Data in the case of a woman aged 50. The diagnosis was stone in the common duct. Autopsy revealed thrombosis of the hepatic artery and of the portal vein. An infarct of the liver was present. There were numerous petechiae.

day it suddenly fell to 25 per cent again, and it remained at about this level despite repeated transfusions and continued vitamin K therapy. The patient subsequently died, and at postmortem examination thromboses of the hepatic artery and portal vein with massive necrosis of the liver were observed. Microscopic examination of the thrombi indicated that they had been deposited at about the time that the fall in the level of plasma prothrombin occurred. The massive hepatic necrosis which followed produced an effect comparable to that seen following partial hepatectomy in animals.

A similar but less acute effect is seen in chart 5, which depicts the course of the plasma prothrombin level in a patient with severe cirrhosis of the liver. In his case the concentration of prothrombin was 70 per cent of normal before treatment with 2-methyl-1, 4-naphthoquinone was begun, but even when more than adequate doses were administered the prothrombin concentration continued to fall until it reached 48 per cent of normal. At operation the liver was found to be markedly cirrhotic and considerably reduced in size.

These 2 cases are chosen from a number illustrating the influence of damage to the liver on the level of the plasma prothrombin and the response to vitamin K, and the group as a whole suggests the significance

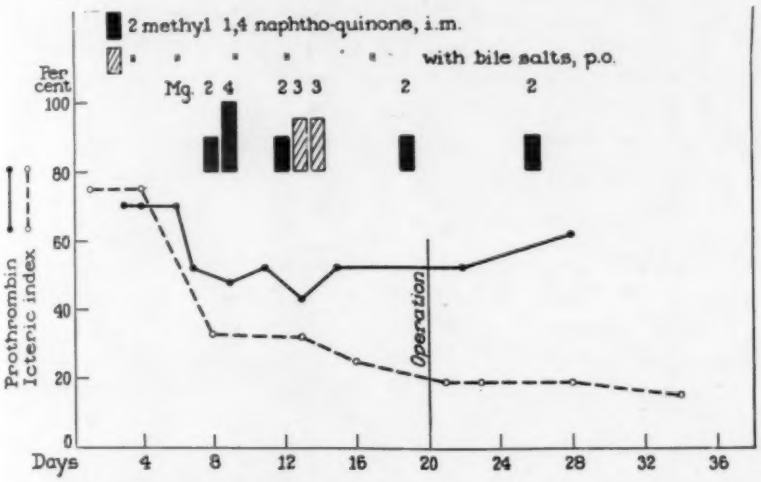

Chart 5.—Data in the case of a man aged 61. The diagnosis was cirrhosis of the liver. Exploratory laparotomy was performed. The hipuric acid test revealed a value of 2.98 Gm. The galactose tolerance test showed 7.3 Gm. excreted. The bromsulfalein test showed a faint trace present after thirty minutes.

of these factors as an indication of hepatic function, at least so far as its prothrombin-forming activity is concerned. Determination of the extent to which this interpretation can be carried clinically awaits further studies, but work now in progress in this clinic lends support to this idea.

SUMMARY

The history of the establishment of a prothrombin deficiency as the cause of the hemorrhagic tendency associated with jaundice and of the significance of vitamin K in the production of this component of the clotting mechanism is briefly traced.

Clinical experience with crude extracts of substances containing the vitamin and later with the highly potent compound 2-methyl-1, 4-naphthoquinone is reported.

Clinical cases are presented confirming various findings concerning the metabolism of vitamin K and prothrombin in animals, as reported in the preceding paper. The important role of the liver is stressed, and evidence is presented indicating that damage to this organ may depress the level of plasma prothrombin and seriously interfere with the response to vitamin K therapy.

INFLUENCE OF FUSION OF THE SPINE ON THE GROWTH OF THE VERTEBRAE

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The frequency of the operation for fusion of the spine has increased markedly in recent years, since its utilization for the treatment of scoliosis. As most fusion operations are performed on children during their active growing period, the question arises as to its influence on the growth in length of the vertebral column. If the fused spinous process should act as a brake on expansion of the corresponding bodies, the restriction of growth would be of considerable significance, particularly when one third or more of the processes are fused at one time.

In order to appreciate this investigation better it may be well to have some definite conception as to the mechanism of normal growth of the bodies of the vertebrae. It has been shown in dogs in some previous experiments that growth in length of the bodies takes place at the epiphysial cartilaginous plates in a manner similar to that of the long bones.[1] It has also been shown that it is possible to stop growth of the vertebral body by destroying the epiphysial plates or to produce deformity by injuring a part of the plate.[2] If fusion of the spinous processes is performed at the time of injury to the epiphysial cartilaginous plates, deformity may be prevented.[3] With normal growth of the body, corresponding changes must take place in the spinous processes and in the laminas. By fusion of the spinous processes, these changes are prevented, and it is of considerable interest to know whether any secondary disturbances of growth occur in the bodies or in the intervertebral disks.

It is believed that growth of the vertebrae in man takes place similarly to that in the dog, in spite of the claims of Schmorl and his followers to the contrary. The reason for this discrepancy of opinion may be the fact that in man the growth of the spine is distributed over fifteen to twenty years. The growth in man of each vertebra over this long period is very small, and therefore there is little demand for a highly

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1. Haas, S. L.: Growth in Length of the Vertebrae, Arch. Surg. **38**:245 (Feb.) 1939.

2. Haas, S. L.: Experimental Production of Scoliosis, J. Bone & Joint Surg. **21**:963 (Oct.) 1939.

3. Haas, S. L.: The Prevention of Deformity of the Spine by Vertebral Fusion, J. Bone & Joint Surg. **22**:157 (Jan.) 1940.

differentiated epiphysial cartilaginous plate. The columns of cartilage in the vertebral bodies of man are rather irregular and are narrow, but they are adequate for purposes of slow growth. On the contrary, for the dog the period of growth is only nine months, and there is a demand for rapid growth, so that there is of necessity a more highly specialized epiphysial cartilage plate. The columns of cartilage are longer and more regular, approaching more nearly those of the long bones, in which growth is rapid.

In an effort to determine the effect of fusion of the vertebrae on growth of the spine, a series of experiments were performed on growing dogs in which the vertebrae were fused by either the Hibbs or the Albee method. Wire markers were placed in the operative area to indicate whether any changes took place during the growth of the animal. In another group of experiments, in addition to the fusion of the spinous processes, the bodies of the vertebrae were exposed through an abdominal approach, and markers were placed in the bodies and epiphyses of the vertebrae for comparative studies of growth.

At the beginning of the experiments roentgenograms were taken for record showing the position and distance apart of the markers. Roentgenograms were also taken at the end of the experimental period to show the final position of the markers. The distances between the markers were measured and compared with those at the time of operation to determine the amount of growth that took place between the markers during the period of observation. Comparative studies were made between growth in the spine and growth in the vertebral bodies. The study of the gross specimens showed the changes in shape of the spine. The cut specimens were studied for changes in the epiphysial plates, the epiphyses, the bodies and the intervertebral disks.

There were 22 experiments: (1) five Hibbs fusions; (2) twelve Albee fusions; (3) three combination Hibbs fusions with placing of markers in the bodies of the vertebrae, and (4) two combination Albee fusions with placing of markers in the bodies of the vertebrae.

HIBBS TYPE OF SPINAL FUSION

There were 5 operations in this series, in which the spinous processes were fused by various modifications of the Hibbs operation.

EXPERIMENT 1.—*Dog 1; age, 4 months; duration of experiment, twenty days.*

Operation.—With ether anesthesia and under sterile conditions an incision was made over the lumbar spinous processes. The spinous processes were exposed, and the muscles were stripped off subperiosteally from the spinous processes of three vertebrae. The spinous processes were interlocked with each other. The articular facets were not destroyed.

Gross Observations.—There was considerable osseous proliferation, considering the short time since the operation. There was a fair amount of fixation in the fused area. The bodies bulged slightly anteriorly.

Growth.—The duration of the experiment was too short to show any disturbance in growth.

EXPERIMENT 2.—*Dog 4; age, 3 months; duration of experiment, thirty-four days.*

Operation.—On March 19, 1935, with the dog under ether anesthesia, an incision was made over the lumbar spinous processes. The muscles were deflected to either side subperiosteally. The articular facets were not destroyed. The spinous processes were interlocked with each other, and bone was raised from the laminas and brought into contact with the laminas from above and below. Two wire markers were placed in the spinous processes. The wound was closed in layers.

Gross Observations.—There was a little fixation of the spine. There was some proliferation of bone between the spinous processes. The articular facets showed no changes, as they were not destroyed. There were no changes in the bodies, and the epiphysial cartilaginous plates appeared normal.

Growth.—There was a slight amount of rigidity in the operative area of the spine. There was a slight increase in distance between the markers. Very little change was seen in the intervertebral disk or the epiphysial cartilaginous plates.

EXPERIMENT 3.—*Dog 5; age, 3 months; duration of experiment, two hundred and five days.*

Operation.—On March 19, 1935, incision was made over the lower part of the thoracic and the lumbar region of the spine. The spinous processes from the twelfth thoracic to the fourth lumbar were exposed. The muscles were stripped from either side. The articular facets were exposed but not destroyed. Sections of bone were raised from the laminas and placed over the facets. The spinous processes from the twelfth thoracic to the fourth lumbar were made to interlock with each other. Wire markers were attached to the spinous processes, after which the wound was closed in layers.

Gross Observations.—There was firm fixation in the operative area of the spine. The spinous processes were connected with new bone. The articular facets were covered with osseous tissue. The articular cartilages of the facets persisted but were thin. When the bodies of the vertebrae were cut through, the epiphysial cartilaginous plates were observed to be narrow, and some appeared almost completely closed. There was an anterior bulging of the bodies.

Growth.—The markers in the operative area of the spine had separated almost as much as the body had grown (fig. 1). This can be explained by the fact that until fusion is firm and soft callus yields, and there is a pulling apart or stretching of osteoid tissue in the operative area. When ossification is complete, there is no further yielding of the tissue and separation of the markers. There was some compression of the intervertebral disk, which takes place when the fused vertebrae tend to prevent expansion of the bodies in the operative area (fig. 2).

EXPERIMENT 4.—*Dog 6; age, 4½ months; duration of experiment, one hundred and sixty days.*

Operation.—On July 9, 1935, an incision was made over the lower part of the thoracic and the lumbar region. The spinous processes were exposed and the muscles deflected to either side subperiosteally. Five articular facets were destroyed on the right side, and the spinous processes were made to interlock with each other. Wire markers were placed in the vertebrae at either end of the operative area. The wound was closed in layers, and a plaster was applied.

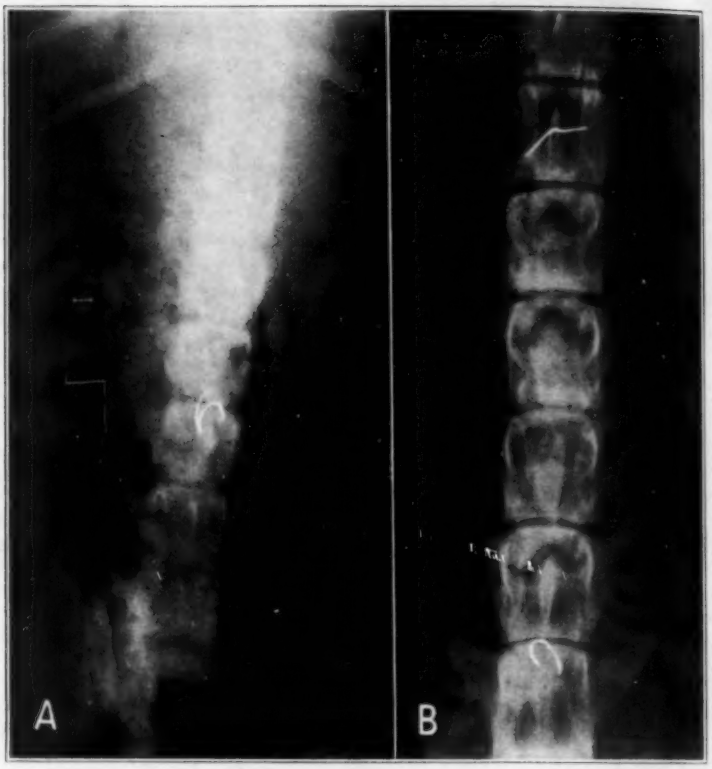

Fig. 1 (experiment 3; dog 5; Hibbs type of fusion; age, 3 months; duration of experiment, two hundred and five days; anteroposterior views).—Roentgenograms, (*A*) at the time of operation and (*B*) at the end of the experimental period, for comparison, showing that separation of markers is almost equal to body growth. Separation continues until fusion is firm enough to resist body growth. The intervertebral disks are narrowed only slightly.

Fig. 2 (dog 5; age, 3 months; duration of experiment, two hundred and five days).—Lateral view, showing a little narrowing of the intervertebral disk and a little tendency to anterior bowing. It is only after fusion is firm that the inhibiting force against growth manifests itself.

Gross Observations.—There was very firm fusion in the operative region of the spine. The articular facets that had been destroyed were firmly fused. Those that had not been destroyed showed very thin articular cartilages. The epiphysial plates could be made out but in some places appeared ossified.

Growth.—The markers in the spinous processes had separated about the same amount as the bodies had increased in length. There was no tendency to lordosis or scoliosis of the spine. The disks were compressed about half their normal width. The epiphysial cartilaginous plates showed some evidence of ossification.

EXPERIMENT 5.—*Dog 7; age, 5 months; duration of experiment, twenty-six days.*

Operation.—On July 16, 1935, an incision was made over the lower part of the thoracic and the lumbar region of the spine. Five spinous processes were exposed, and the muscles were deflected to either side. Three of the articular facets were destroyed, and bone was thrown down from the laminas on the remainder. The spinous processes were made to interlock with each other, after which the wound was closed in layers.

Gross Observations.—There was beginning fusion of the spinous processes and laminas in the operative region, with definite fixation of the spine. The articular facets which had been destroyed showed early signs of fusion. The epiphysial cartilaginous plates appeared normal. There was a little tendency to anterior bulging of the bodies.

Growth.—At the end of twenty-six days no significant changes were made out.

CONCLUSION ON HIBBS TYPE OF FUSION

After the Hibbs type of spinal fusion it was found that the markers placed in the spinous processes operated on had separated in some experiments almost as much as the body had grown. This separation was due to the fact that as the bodies of the vertebrae grow in length the soft callus in the spinous processes operated on yields to the growing forces. As soon as the callus becomes firm there is no more separation of the markers. There is some narrowing of the intervertebral disk and of the epiphysis, particularly at the posterior parts, but it is not marked unless there is an experimental period of considerable length. This narrowing of the disk and epiphyses is due to compression, which results when the fused spinous processes prevent the normal longitudinal expansion of the growing bodies of the vertebrae.

ALBEE TYPE OF SPINAL FUSION

In this group there were 12 experiments, in which the spine was fused by the Albee method or by some modification of it.

EXPERIMENT 6.—*Dog 1; age, 6 months; duration of experiment, three hundred and fifty days.*

Operation.—On Oct. 20, 1936, an incision was made from the first to the fourth lumbar spinous process. The muscles were deflected subperiosteally from the spinous processes. A bone graft was removed from the tibia and placed in the split spinous processes of the lumbar vertebrae. Wire markers were placed in the spinous

processes at either end but not attached to the graft. The wound was closed in layers. A plaster of paris cast was applied.

Gross Observations.—There was solid fusion in the operative region of the spine, giving good fixation. The cartilages of the articular facets were very thin. The epiphysial cartilaginous plates were ossified. There was definite bulging of the bodies of the vertebrae anteriorly.

Growth.—The markers had separated a little more than the body had grown. The growth of the bodies was relatively slight, as the animal was almost three-fourths grown at the time of operation.

EXPERIMENT 7.—*Dog 2; age, 5 months; duration of experiment, sixty-one days.*

Operation.—On Oct. 27, 1936, an incision was made over the lower lumbar portion of the spine, and the spinous processes from the second lumbar to the sacrum were exposed. The muscles were then stripped from the processes subperiosteally. A bone graft was removed from the left femur and placed in the split spinous processes. Wire markers were placed at either end and in the center of the graft. The wound was then closed in layers.

Gross Observations.—There were good fusion in the operative area and firm fixation. There was considerable proliferation of bone about the graft. The markers were found embedded in the new bones. The bone graft could still be made out but was firmly anchored to the spinous processes. The articular facets were easily made out. On longitudinal section the epiphysial cartilage plates were found to be normal in appearance. There was broadening of the intervertebral disks anteriorly, and the bodies projected anteriorly.

Growth.—The bodies had increased in size, but the markers, which were attached to the graft, had not separated. There was no interstitial growth in the graft, so that the markers could not separate. There were some compression of the disks and bulging of the bodies anteriorly.

EXPERIMENT 8.—*Dog 3; age, 5 months; duration of experiment, two hundred and sixteen days.*

Operation.—On Nov. 31, 1936, an incision was made over the lumbar spinous processes and was extended down to the upper end of the femur. The spinous processes from the third lumbar to the first sacral were exposed. The muscles were deflected subperiosteally and the spinous processes split in half. Three pieces of a femoral bone graft were placed in the split spinous processes from the third lumbar to the first sacral vertebra. Wire markers were attached to the spinous processes. The wound was closed in layers, and a plaster spica was applied to the body and limb.

Gross Observations.—There was good fusion of the bone graft with the spinous processes, with firm fixation of the spine. The articular facets showed evidence of spontaneous fusion. The intervertebral disks were a little broader anteriorly. The epiphysial cartilaginous plates were thin and beginning to ossify in some places.

Growth.—The growth of the body had been relatively small. The markers had separated almost as much as the body had grown. There was some narrowing of the intervertebral disks. There was a normal lumbar curve to the spine.

EXPERIMENT 9.—*Dog 4; age, 5 months; duration of experiment, five days.*

Operation.—On Nov. 10, 1936, an incision was made over the lower lumbar spinous processes, from which, after exposure, the muscles were deflected subperi-

osteally from both sides. The spinous processes were split to one side, and two bone grafts removed from the fibula were placed end to end in the crevice. The two pieces were held in place by wires fastened to the spinous processes. The wound was closed in layers, and a plaster spica was applied.

Gross Observations.—There was good healing. No changes were made out except early signs of wound healing.

Growth.—The duration of the experiment was too short to show any changes in growth.

EXPERIMENT 10.—*Dog 5; age, 5½ months; duration of experiments, thirteen days.*

Operation.—On Nov. 17, 1926, an incision was made over the lumbar spinous processes. The spinous processes were exposed and the muscles deflected to either side subperiosteally. The spinous processes were split in the sagittal plane, and in the crevice two pieces of bone from the fibula were placed. Wire markers were anchored to the spinous processes at either end.

Gross Observations.—The wound had healed normally. There were no changes except beginning organization of blood clots and healing.

Growth.—The period of observation was too short to show any changes in growth.

EXPERIMENT 11.—*Dog 6; full grown; duration of experiment, three hundred and forty-one days.*

Operation.—On Dec. 1, 1936, an incision was made over the lumbar spinous processes, from which, after exposure, the muscles were stripped off from the sides subperiosteally. The spinous processes were split in half, and several grafts removed from the fibula were placed in the split spinous processes. Wire markers were put on the spinous processes at either end.

Gross Observations.—There was strong fusion of the grafts with the spinous processes, giving excellent fixation to the spine. There was no tendency to bulging anteriorly. Some of the articular facets showed spontaneous fusion. The epiphysial cartilage plate was ossified.

Growth.—There was no growth of the body, and no separation of the markers took place. The animal was full grown at the time of the operation. There was no ossification or narrowing of the disk. The epiphysial cartilage plates had ossified. Firm fushion of the spinous processes had taken place.

EXPERIMENT 12.—*Dog 7; full grown; duration of experiment, one hundred and seventy-four days.*

Operation.—On Dec. 15, 1936, an incision was made over the lumbar spinous processes. The muscles were deflected subperiosteally to either side, and the spinous processes were split in half. Several bone grafts were removed from the ilium and fitted into the split processes.

Gross Observations.—There was good fusion in the operative region, with strong fixation of the vertebrae. The articular facets could be made out, although some appeared to be fusing. A few remnants of the epiphysial cartilaginous plates were present, but the majority were completely ossified. There was no bulging outward; in fact, there was some tendency to rounding of the spine.

Growth.—No growth of the bodies or separation of the markers took place, because the animal was full grown at the time of the operation. There were no changes in the intervertebral disks or the vertebral bodies. This experiment and the previous one served as controls to those performed on growing animals.

EXPERIMENT 13.—*Dog 8; age, 3 months; duration of experiment, one hundred and twenty-six days.*

Operation.—On June 8, 1937, an incision was made over the lumbar spinous processes. The spinous processes were exposed and the muscles deflected to either side subperiosteally. Three of the spinous processes were split longitudinally, and a bone graft removed from the ilium was fitted between them.

Gross Observations.—There was firm fusion of the graft with the spinous processes. The graft could be distinguished in the new bone. The articular facets were thin. The epiphysial cartilaginous plates were present but appeared to be undergoing ossification. There was a little anterior bowing of the bodies. The intervertebral disks were broader anteriorly.

Growth.—The spines were connected with a bony bridge. There was some bulging anteriorly of the bodies of the vertebrae. There was separation of the markers, but only to about half the amount of the body growth. The disks were slightly narrower in the center and posteriorly. There was almost complete bony bridging across the disk posteriorly in some places. The epiphysial plates were very thin and almost absent in the fused areas.

EXPERIMENT 14.—*Dog 9; age, 3 months; duration of experiment, one hundred and twenty-six days.*

Operation.—On June 8, 1937, an incision was made over the lower spinous processes. The processes were exposed and the muscles deflected to either side subperiosteally. A bone graft was removed from the femur and placed alongside the exposed spinous processes. The articular facets of the vertebrae caudad to this area were destroyed. Wire markers were attached to the vertebrae at either end, after which the wound was closed in layers.

Gross Observations.—There was firm fusion of the spinous processes with the graft. The articular facets were not fused. The epiphysial cartilaginous plates were just visible, as the greater parts appeared to be undergoing ossification. The intervertebral cartilages were wider anteriorly, and there was definite bowing anteriorly of the bodies. The portion in which the facets were destroyed was likewise fused firmly, as were the facets.

Growth.—There was firm fusion of the spinous processes in the operative area. The markers which were in the spinous processes had separated to some extent but much less than the body had grown (fig. 3). There was some anterior bulging of the bodies. The disks were narrower than normal in the fused area, and one disk was almost completely ossified (fig. 4). The epiphysis tended to be wedge shaped. The epiphysial cartilaginous plates were almost entirely closed throughout the spine.

EXPERIMENT 15.—*Dog 10; age, 4 months; duration of experiment, one hundred and eleven days.*

Operation.—On June 23, 1937, an incision was made over the lumbar spinous processes. After the processes were exposed, the muscles were stripped from either side subperiosteally. A bone graft removed from the femur was anchored to the spinous processes with a wire at either end.

Gross Observations.—There was strong fusion in the operative area. The bone graft could just be made out in the mass of new bone. The articular facets were narrow, with thinning of the articular cartilages. The epiphysial cartilaginous plates were present but slightly narrower than normal and in some places showed

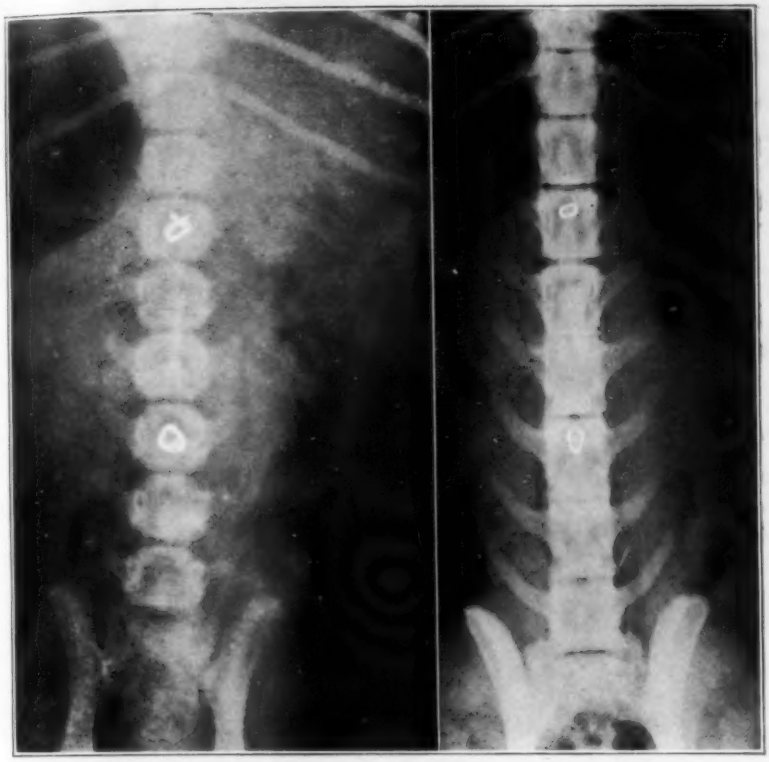

Fig. 3 (experiment 14; dog 9; age, 4½ months; duration one hundred and twenty-six days; Albee type of fusion).—Anteroposterior roentgenograms showing much greater growth of the body than separation of the markers. Fusion took place more quickly than with the Hibbs type of operation, so that the markers in the spinous processes did not separate so much as the body of the vertebrae increased in size. After fusion the resistance to expansion causes compression of the intervertebral disk and anterior bowing of the bodies.

Fig. 4 (experiment 14; dog 9; age, 4½ months; dura'ion of experiment, one hundred and twenty-six days).—The lateral view shows the anterior bulging of the bodies with a tendency to lordosis. The fused spinous processes offer resistance to expansion longitudinally, and the body growth protrudes toward the place of least resistance which is anteriorly in the direction of the abdominal cavity. Note the compression of the disk which is greater posteriorly. In the anteroposterior view the narrowing appears to occupy the entire disk, while in fact, as is shown in the lateral view, it is wide anteriorly and narrow posteriorly.

beginning ossification. The disks were thinner posteriorly than anteriorly, and there was bowing forward of the bodies of the vertebrae.

Growth.—The markers, which were attached to the graft, were prevented from separating. There was a considerable increase in size of the bodies of the vertebrae. The disks were moderately compressed. The epiphysial cartilaginous plates showed signs of ossification about the periphery. The last lumbar vertebra showed a wedge-shaped disk, most likely caused by extreme pressure posteriorly.

EXPERIMENT 16.—*Dog 11; aged, 4 months; duration of experiment, two days (dog died).*

Operation.—On June 23, 1937, an incision was made over the lumbar spinous processes. Four of the processes were exposed and the muscles stripped off subperiosteally from both sides. A bone graft was removed from the femur and placed alongside the denuded processes. The articular facets were destroyed. The wound was sutured in the usual manner, and a plaster cast was applied.

Gross Observations.—The grafts were found in place, and the blood clots were beginning to organize.

Growth.—There were no changes at this early period.

EXPERIMENT 17.—*Dog 12; age, 4 months; duration of experiment, one hundred and eleven days.*

Operation.—On June 23, 1937, an incision was made over the lumbar spinous processes. Dissection was carried down the processes, and the muscles were stripped subperiosteally from either side. A bone graft removed from the femur was anchored to the lower spinous process with a wire. A wire marker was placed on the upper spinous processes but not fastened to the graft. The articular facets were curetted on one side.

Gross Observations.—The bone graft was well united to the spinous processes, producing firm fusion. The destroyed articular facets on one side showed fusion. The epiphysial cartilaginous plates could be made out but were a little thinner than normal in the fused area, and some showed beginning ossification. The epiphyses were wedge shaped, being broader anteriorly. The intervertebral disks were not changed, but there was definite anterior bowing of the bodies.

Growth.—The markers had separated, but much less than the body had grown. There was a definite anterior bulging of the bodies of the vertebrae. The spinal canal was widened. The disks were compressed and at the posterior end were narrower, and in some places there was almost bony fusion. The epiphysial cartilaginous plates showed evidence of ossification posteriorly, and the epiphyses were narrower posteriorly.

CONCLUSION ON ALBEE TYPE OF FUSION

There is more rapid fusion with the Albee type of operation in which a bone graft is inserted into the spinous process than in the Hibbs type of operation. Consequently, there is less separation of the markers in the spinous process than is observed with the Hibbs type. There is also a greater disproportion between separation of the markers and body growth with the Albee than with the Hibbs type. There are more marked changes in the intervertebral disk and in the epiphyses

and epiphysial plates, because with earlier firm fusion of the spine there are greater hindrance of expansion of the bodies by growth and more compressive force. The bodies, being hindered from longitudinal expansion, tend to project anteriorly toward the place of least resistance, normally away from the fixed part of the spine.

COMBINATION HIBBS FUSION AND PLACING OF MARKERS IN BODIES OF VERTEBRAE

In this series there were 3 experiments in which the Hibbs type of spinal fusion was performed at one operation and, after an interval to allow healing of the wound, a second operation was performed, in which the bodies of the vertebrae were exposed through an abdominal incision.

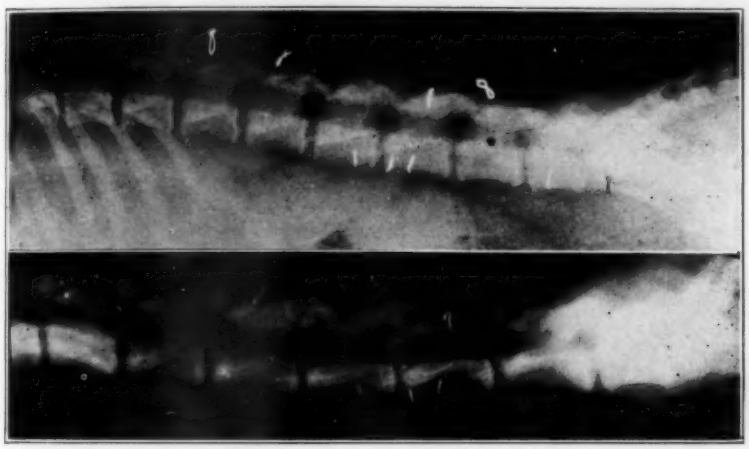

Fig. 5 (experiment 18; dog 7; age, 3⅓ months; Hibbs fusion with markers in the bodies of the vertebrae; duration of experiment, one hundred and fifty-one days).—The lateral views show the markers in the spinous processes and in the bodies. The markers in the area of fusion have separated almost as much as the body has grown. Notice how the markers in the bodies have separated according to the presence of one or more intervening epiphysial cartilage plates between them. There is very little narrowing of the intervertebral disk and very little tendency to anterior bowing of the bodies. The roentgenogram at the top was taken before operation; that at the bottom, after operation.

Markers were placed in the bodies to serve as a means of determining changes in growth to compare with markers in the spinous processes operated on.

EXPERIMENT 18.—*Dog 7; age, 3½ months; duration of experiment, one hundred and fifty-one days.*

Operation, First Part.—On March 3, 1936, an incision was made over the spinous processes of the lower lumbar vertebrae. The processes were exposed

and the muscles deflected to either side subperiosteally. The articular facets of three of the vertebrae were destroyed. Sections of bone were thrown over the facets from the laminas. The spinous processes were not interlocked. Markers were placed at either end of the operative area and on the spinous processes above and below those operated on. The wound was closed in layers, and plaster was applied.

Operation, Second Part.—On March 25, through a midabdominal incision, the intestines were exposed and walled off until the posterior abdominal wall was exposed. The abdominal aorta and vena cava were exposed and gently retracted to one side. Care was taken not to injure the ureter. The periosteum was incised, and the desired portion of the bodies of the vertebrae was exposed. A wire marker was placed in the body of three vertebrae and in the middle one. An additional marker was placed in the epiphysis. The gauze packs were removed, and the abdominal incision was closed in layers.

Gross Observations.—There was fairly firm fusion but not complete bony union of the spinous processes. There was beginning ossification of some of the facets. There was no gross narrowing of the bodies. The epiphysial cartilaginous plates were present and were a little thin but they differed little from those opposite the nonfused area. The epiphysis did not show any change. The disks were a little narrower than normal posteriorly. The bodies showed anterior bowing.

Growth.—There had been a greater growth of the body than separation of the markers in the spinous processes. There was not much compression of the disks. There was little lordosis. The markers in the bodies showed separation, the amount depending on the number of intervening epiphysial plates (fig. 5). As far as could be determined, there was just as much growth of the bodies in the fused areas as outside.

EXPERIMENT 19.—*Dog 10; age, 3½ months; duration of experiment, eighty-four days.*

Operation, First Part.—On March 10, 1938, an incision was made in the midabdominal line; the peritoneum was incised with exposure of the intestines, which were walled off with gauze. With careful avoidance of the large vessels and ureters, the bodies of the lumbar vertebrae were exposed. After an incision had been made through the periosteum, it was stripped off to either side, the epiphysial plate being exposed. The epiphysial cartilaginous plate of the middle vertebrae was injured, and markers were placed in the epiphysis. In the lower vertebra a hole was bored in the body and a marker placed in the hole. In the upper vertebrae a marker was placed in the body and in the epiphysis.

Operation, Second Part.—On March 25 an incision was made over some of the spinous processes, which were exposed. The muscles were deflected to either side subperiosteally, after which the articular facets were destroyed, bone was thrown up from the laminas and the spinous processes were made to interlock. The wound was then closed in layers.

Gross Observations.—There was firm fusion of the spinous processes, and the articular facets appeared fused. The epiphysial cartilaginous plates were normal in structure. The intervertebral disks were thinner posteriorly and broader on the anterior surface. There was no definite bulging of the bodies anteriorly.

Growth.—Body growth was greater than separation of the markers except where the body had been injured or the epiphysial plate destroyed. All the intervertebral disks were narrower, and there was a tendency for bony bridging across

one disk. There was not much tendency to kyphosis, in spite of the fact that there was extensive destruction of the epiphysial plate and body.

EXPERIMENT 20.—*Dog 11; age, 3½ months; duration of experiment, three hundred and fifty-one days.*

Operation, First Part.—On March 14, 1938, through a mid-abdominal incision, the viscera were exposed and walled off. Care was taken not to injure the large vessels, and the bodies of the vertebrae were exposed. The periosteum was then incised and stripped off over a small area so that the epiphysial cartilaginous plates could be identified. Markers were placed in the bodies of three vertebrae. In the two lower vertebrae sections of bone were turned up from the bodies and brought into contact with one another over the intervertebral disk. The packing was removed and the abdominal wall closed in layers.

Operation, Second Part.—On March 25 an incision was made over four spinous processes, after which the muscles were stripped off subperiosteally from either side. The articular facets were destroyed and the spinous processes made to interlock with each other. The wound was closed in layers.

Fig. 6 (experiment 20; dog 11; age, 3½ months; Hibbs fusion in conjunction with bridging between the bodies of the vertebrae; duration of experiment, three hundred and fifty-one days).—Notice that besides the Hibbs fusion of the spinous process there is a bony bridge between the bodies of two vertebrae. This acts as an accessory supporting measure to prevent deformity besides decreasing longitudinal expansion of the bodies of the vertebrae.

Gross Observations.—There was fairly firm fusion of the spine but not complete osseous bridging between the spinous processes. The articular facets were irregular in form, with some proliferation about them but no osseous fusion. Some of the disks appeared narrower posteriorly. The epiphysial cartilaginous plates were ossified. There was no anterior bulging of the bodies.

Growth.—There was an anterior bony bridging between the bodies where the sections of bone had been thrown across the disk (fig. 6). This caused a considerable hindrance of growth. The bodies outside this area had increased normally and to a greater extent than had separation of the markers in the fused area. There was no anterior bulging in the fused area, as it was prevented by the anterior bridge of bone between the bodies of the vertebrae. The epiphysial cartilaginous plates in the operative as well as in the nonoperative area were ossified.

CONCLUSION ON COMBINATION HIBBS FUSION AND PLACING OF MARKERS IN THE BODIES OF THE VERTEBRAE

The combination operations gave a clearer idea of the relative amount of growth of the bodies and separation of the markers in the spinous processes operated on. The findings were practically the same as with the simple Hibbs fusion, in that separation of the markers in the fused spinous processes proceeded with growth of the bodies until union was firm, after which growth was almost entirely confined to the bodies. There was only a moderate amount of compression of the disk and bodies posteriorly.

COMBINATION OF ALBEE FUSION OF SPINE AND PLACING OF MARKERS IN BODIES

There were 2 operations in which the Albee type of fusion was performed and at a later date markers were placed in the bodies of the vertebrae through an abdominal approach.

EXPERIMENT 21.—*Dog 8; age, 3½ months; duration of experiment, one hundred days.*

Operation, First Part.—On March 3, 1938, the spinous processes of three lumbar vertebrae were exposed through an incision in the lumbar region. The muscles were deflected to either side, and the spinous processes were split in half. A bone graft removed from the femur was placed between the split processes. One pair of articular facets were destroyed below this area. Markers were placed at either end and on one of the spinous processes below the last vertebrae operated on. The wound was closed in layers, and plaster was applied.

Operation, Second Part.—On March 21, through an abdominal incision, after retraction of the viscera the bodies of the lumbar vertebrae were exposed. Markers were placed in the bodies of three vertebrae and an additional marker in the epiphysis of the lower vertebrae. The wound was closed in layers.

Gross Observations.—There was firm fusion of the spinous processes. The articular facets were fused on one side. The epiphysial cartilaginous plates showed no gross changes. The epiphyses were wedge shaped, being broader anteriorly. The intervertebral disks were thin posteriorly and broad anteriorly. The bodies of the vertebrae bowed anteriorly.

Growth.—The markers in the spinous processes, not being attached to the graft, separated until fusion was firm. The markers in the bodies had separated, except those that had no intervening epiphysial plate. There was bulging forward of the bodies, with greater growth anteriorly (fig. 7). The disks were narrowed posteriorly. The epiphysial plates were not so prominent in the fused area as outside it.

EXPERIMENT 22.—*Dog 9; age, 3⅓ months; duration of experiment, two hundred and sixty-one days.*

Operation, First Part.—On March 7, 1938, through a midline abdominal incision, the intestines were exposed and walled off. The bodies of the vertebrae were then exposed and the periosteum incised. Markers were placed in the bodies of three vertebrae and in two epiphyses of adjoining vertebrae.

Operation, Second Part.—On March 25 an incision was made over the lumbar spinous processes. The spinous processes were exposed and the muscles deflected subperiosteally to either side. Several bone grafts were removed from the upper end of the femur and wedged into the spinous processes. Markers were placed in the base of the spinous processes at either end and looped over the middle of the graft. A plaster spica was applied.

Gross Observations.—There was osseous fusion of the spinous processes. The articular facets showed no gross changes. The epiphysial cartilaginous plates had fused. There were no gross changes in the disk and bodies, and the bodies did not project forward.

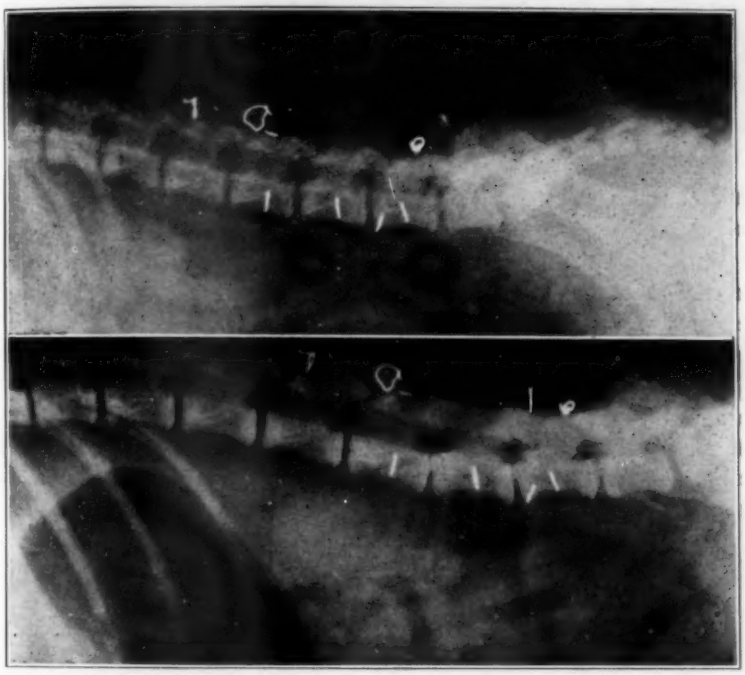

Fig. 7 (experiment 21; dog 8; age, 3½ months; Albee fusion with markers in the bodies of the vertebrae; duration of experiment, eighty-four days).—Lateral views. The markers in the fusion area have separated much less than the body has grown. Body growth is being interfered with, as is shown by the narrowing of the intervertebral disk posteriorly and the lordosis of the bodies as they bulge anteriorly toward the place of least resistance. The growth between the markers in the bodies varies with the presence of intact epiphysial cartilage plates between them. Notice the wide anterior part of the intervertebral disk and the narrow posterior portion. The roentgenogram at the top was taken before operation; that at the bottom, after operation.

Growth.—The markers in the spines had separated very little. There was much greater growth of the bodies. The epiphysial plates were fully ossified. The intervertebral disks had been compressed posteriorly, but the bulging anteriorly was not very marked.

CONCLUSION ON COMBINATION ALBEE FUSION AND PLACING OF MARKERS IN BODIES OF VERTEBRAE

This series of combination Albee experiments substantiate the findings with the simple Albee fusion operations. They give a clearer conception of the changes in growth in the bodies of the vertebrae. It is seen that whenever there is an epiphysial cartilaginous plate between two markers there is a separation of the markers, due to the fact that longitudinal growth takes place at the epiphysial cartilaginous plate. The inhibiting forces of fusion of the spine cause narrowing of the epiphysis posteriorly and compression of the posterior part of the intervertebral disk and bowing of the bodies anteriorly.

COMMENT

It is important to keep in mind that in the dog the period of growth is limited to between eight and nine months, so that in the animal operated on at 2 months of age there are approximately about two hundred and ten days more of growth.

With the Hibbs type of operation the markers in the fused spinous processes separated almost as much as the bodies increased in size or the markers in the bodies separated. The markers in the fused spine separated because it took a considerable period for the spinous processes to become firmly fused and not be subjected to the traction force of the growing vertebral bodies. In other words, the growing vertebral bodies served as a lengthening apparatus during the period in which the callus was soft. Just as soon as fusion was firm in the spinous processes, there was no yielding in the fused spine to the growing forces of the bodies, and no further separation of the markers took place. When fusion was firm in the spinous processes, the reverse took place, and the fused spine exerted a hindering force on body growth. This is evidenced by the compression of the disk, the bulging anteriorly of the bodies, the tendency to wedging of the epiphysis and the premature ossification of the epiphysial plates.

With the Albee type of fusion there was much less separation of the markers in the spinous process. This was due to an earlier firm fusion of the spines, and on that account there was less chance for growth of the body to expand the fused area. Just how much disturbance in body growth takes place is difficult to evaluate. There is considerable evidence that the inhibitory forces are strong, as evidenced by a tendency for the bodies to bend anteriorly. There are also thinning of the disk and ossification, especially at the posterior part of the disk. The epiphysis is wedge shaped, with the apex posterior. The epiphysial plates are prematurely ossified. It is this wedging of the bodies with narrowing and ossification of the disk at the posterior end that give the

characteristic picture of narrowing of the intervertebral disk, which may be seen in the anteroposterior roentgenogram of any fused spine. On gross examination, definite widening and bulging of the disk anteriorly are seen in these same specimens, which in the roentgenogram appear narrow because of compression of the posterior portion.

With the Albee type of operation, if the markers are attached to the graft there is no separation of the markers, because there is no interstitial growth in a graft. The grafted region may be increased to some extent if bone is added to either end by a proliferation of osseous tissue adjoining the grafted area.

In the series of experiments in which markers were attached to the spinous process and at a second operation on the same animal the markers were placed in the bodies through an abdominal incision, a somewhat clearer idea was obtained of the body growth and a better opportunity was provided for comparative study of changes in the bodies and in the fused spinous processes. It was seen that the markers in the spinous processes separated up to the time of firm fusion of the spinous processes. The body markers separated as long as body growth took place. It is difficult to determine the exact amount of inhibition in body growth after firm fusion of the spinous processes, but there must have been a considerable hindering force at work after this firm fusion occurred, because the bodies tended to bulge anteriorly, and lordosis took place. There were also compression of the intervertebral disk, wedging of the epiphysis and changes in the epiphysial cartilage plates indicative of restriction to longitudinal expansion.

Unfortunately, it is impossible to correlate the findings in animals with what takes place in human beings, because of the long period (up to eighteen years) of growth in man as compared with the short growth period (about nine months) for animals. One would expect more inhibition of growth and more changes in the disk and bodies, because there is a much longer period for these forces to work, and the amount of normal growth is greater in man.

Many interesting questions arise from the clinical as well as from the experimental side. Although it is not within the scope of this paper to take up these problems, there is sufficient clinical evidence to show a corrective or preventive property after fusion. Secondary compensatory increase in growth outside the fused area is one of the other problems that needs investigation. The effect of fusion of the spine on a very young growing person needs careful study. It is possible that in some cases it may aggravate rather than decrease the deformity. Therefore, it is important to select the proper region of the spine, the correct age for fusion and the proper number of vertebrae to fuse. It is possible that if more attention is paid to these details better results may be obtained in the future treatment of scoliosis.

CONCLUSIONS

Fusion of the spinous processes in animals causes definite changes in the growing vertebral bodies. Although body growth goes on, there are inhibitory forces at work, as is evidenced by the tendency of the bodies to bulge anteriorly, the tendency to lordosis, the tendency to compression of the intervertebral disk, especially posteriorly, and the tendency to premature ossification in the epiphysial cartilaginous plates. Advantage may be taken of distortion and inhibitions of growth caused by fusion of the spinous processes for the correction of existing deformities of the growing spine—in cases of tuberculosis, to correct the kyphosis by the production of lordosis. In cases of scoliosis, aside from the usual fixation after correction, it is possible that fusion can be produced outside the curve or in certain parts of an existing curve to exert a corrective influence or to prevent increase of early scoliosis more satisfactorily than is possible at present. The intra-abdominal approach, with fusion between the bodies or destruction of the epiphysial cartilaginous plate, if found practical, may help solve some of the problems of scoliosis, hemivertebrae and fracture and disease of the vertebral bodies.

EXTENSIVE PLEXIFORM NEUROFIBROMATOSIS OF THE SCALP AND PINNA

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The purpose of this paper is to describe a recent experience with a rare type of benign tumor of the scalp, to narrate its life history with particular reference to alterations in its histologic characteristics and to describe the operative procedure employed in an attempt to improve the disfigurement resulting from the tumor.

REPORT OF A CASE

A 21 year old clerk was admitted to the neurosurgical service of the Kings County Hospital on Nov. 16, 1938. His chief complaints referred to a marked redundancy of the scalp overlying the left side of the head and to a downward sagging of the left ear. Except that the patient's mother had had a convulsive disorder during childhood, the family history was noncontributory. The past personal history indicated that measles had been the only childhood exanthematous disease contracted by the patient. His health otherwise had been excellent until the onset of the present illness, during his ninth year. At this time the first evidences of a curvature of the upper part of the thoracic portion of the spine were noted. During the ensuing year this condition advanced insidiously. Examination at one of the local hospital dispensaries revealed in addition to kyphoscoliosis of the thoracic portion of the spine a tumor of the scalp, just above the left ear. This was described as equal in area to a 25 cent piece and feeling "like a mass of small glands." The patient was referred into the hospital for further study on Sept. 13, 1928, and there clinical, laboratory and roentgen examinations failed to demonstrate the existence of glandular, enteric, osseous or pulmonary tuberculosis. Osteomyelitis of the spine similarly appeared capable of being ruled out. The films of the skull revealed a zone of rarefaction approximately ¾ inch (1.9 cm.) in diameter and corresponding in position to the mass on the scalp. Late in September, an operation was carried out, with excision of the tumor of the scalp and rongeuring away of the immediately subjacent portion of the left vault. A microscopic specimen of the scalp tissue removed at this time (fig. 1) was made available through the courtesy of Dr. Leo Davidoff. A histologic diagnosis of fibroma of the scalp was made. The record bore no information with reference to the pieces of bone removed.

During the next three years, efforts to improve the kyphoscoliosis by use of plaster of paris body casts and spinal braces were carried out but were apparently ineffective. Therefore, spinal fusion was performed in June 1931, the spine being fixed from the sixth thoracic to the second lumbar vertebra inclusive. After

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the operation the patient's general health remained satisfactory except that his nutritional state required special attention. No advance in the kyphoscoliosis was noted from this time on.

In July 1933, however, a lumpy mass appeared on the left side of the scalp, in the neighborhood of the scar of the previous operation. The clinical features of this mass were closely similar to those of the tumor extirpated in 1928. A steady extension of the growth was noted, so that by early in the year 1936 the

Fig. 1.—Photomicrograph (hematoxylin and eosin; × 90) of a specimen of scalp obtained at the time of the first operation (September 1928). The section shows young fibrous tissue with abundant fibroblastic cells and relatively poorly developed fibrils of the collagenous type. The blood vessels are few, and their walls, especially the muscularis, are poorly formed. Degenerative features are absent.

scalp overlying the entire left side of the vault became thickened and redundant, hanging in heavy, loose folds. The adjacent tissues of the upper part of the left side of the neck were similarly implicated by the growth. Between 1935 and 1938 there supervened hypertrophy of the left pinna and progressive sagging of the external ear. During this period the active growth of the scalp somewhat

slackened. Tenderness, pain and a tendency to ulceration were conspicuously absent throughout the history. From 1933 to 1935 the patient was treated for a discharge from the left ear. The records do not indicate whether it was clearly established that this discharge resulted from chronic otitis media. The skin of the external canal was described as eczematous. Boric acid douches were employed, and the discharge entirely subsided after two and one half years. Up to the present there has been no recurrence of this condition. At the time of his coming to the dispensary of the Kings County Hospital, in the fall of 1938, the patient's greatest concern was with the social embarrassments arising in relation to his appearance.

Physical examination disclosed the patient to be fairly well developed, affable and intelligent, with a striking asymmetry of the facies (fig. 2). The scalp hung in loose folds from the left side of the head. The left ear was generally enlarged and thickened to approximately one-third again the size of its fellow. The skin of the external meatus was so thickened that the canal was all but occluded. The subcutaneous tissues of the posterior aspect of the left pinna were much hypertrophied and caused the ear to stand out prominently from the head. In addition, the pinna was displaced downward onto the neck so that its uppermost rim was visibly below the level of the tragus of the right ear. Palpation demonstrated that the redundant portion of the scalp varied in thickness between two and four times that of the normal (right) side. The cutaneous surface was soft and smooth, and the growth of hair was somewhat less vigorous over the redundant portion of the scalp than elsewhere. When the tissue was rolled between the finger tips it felt irregular, gristly and much like a bag of worms. Altogether, the cutaneous lesion implicated the posterior frontal, temporal, parietal and occipital regions of the left side of the scalp and the uppermost portions of the posterior triangle of the neck. A vertical scar 1 inch (2.5 cm.) in length was visible over the left posterior parietal region. Beneath this could be palpated a bony defect roughly circular in outline and equal in area to a 25 cent piece. Within this defect a pulsatile sensation corresponding to the circulatory impulses of the underlying brain could be felt. There were rotatory kyphoscoliosis of the thoracic and lumbar levels of the spine and a corresponding deformity of the thoracic basket. The scar of the spinal fusion operation was well healed. General physical examination otherwise gave negative results. There were no positive neurologic findings. The temperature, pulse rate and respirations were normal, and the blood pressure in millimeters of mercury was recorded as 124 systolic and 100 diastolic.

Urinalysis revealed no albumin, dextrose or significant microscopic abnormalities. The hemoglobin content of the blood was 90 per cent (Sahli), and the red blood cells numbered 5,600,000 per cubic millimeter. There were 8,700 white blood cells per cubic millimeter, of which 68 per cent were polymorphonuclear leukocytes and 32 per cent lymphocytes. The value for blood urea was 39 mg., that for creatinine 1.26 mg. and that for sugar 106 mg. per hundred cubic centimeters. Examination of the serum revealed the value for calcium to be 11 mg. and that for combined cholesterol 133 mg. per hundred cubic centimeters. The Wassermann reaction of the blood was negative. Roentgenograms of the skull revealed nothing unusual except for the bony defect of the left parieto-occipital region resulting from the operation in 1928. This was slightly greater than 1 inch (2.5 cm.) in diameter. The lung fields were clear.

Operation was carried out on Dec. 1, 1938, with the region under local procaine hydrochloride anesthesia. The essential steps of the procedure are illustrated in figure 3. A strip of fascia lata measuring approximately ⅞ by 4½ inches (2.2 by

11.3 cm.) was first obtained from the right thigh. A large circumlinear cutaneous incision was then made in the left side of the scalp, beginning anteriorly at the temporofrontal region and sweeping up to the vertex and backward to a point just lateral to the external occipital protuberance. This was carried deep to the bone. A second and lower incision, roughly corresponding to this, was

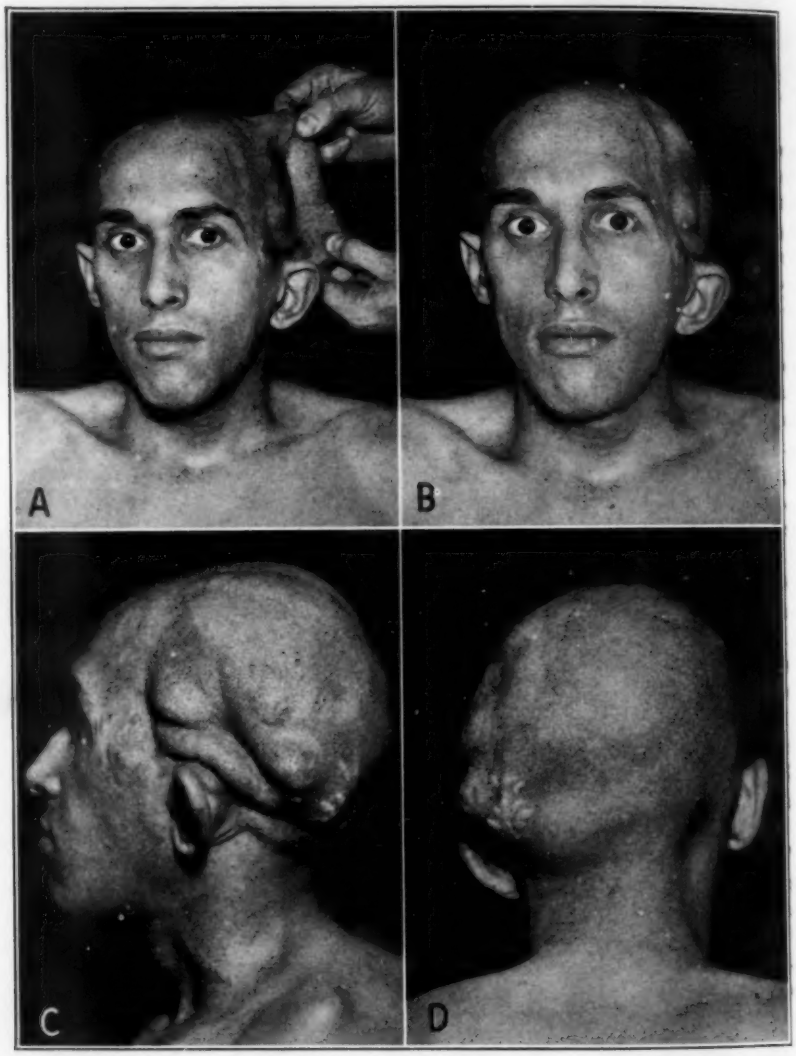

Fig. 2.—Preoperative photographs illustrating the thickening and redundancy of the left side of the scalp and the downward displacement and forward turning of the left pinna. In the lateral (*C*) and posterior (*D*) views the healed scar resulting from the operative procedure in 1928 is clearly visible.

fashioned so as to remove the redundant portion of scalp. A third incision in the scalp was made just above and behind the left pinna (fig. 3 *A*). The postauricular tissues were undermined, and a dense mass of vascularized white fibrotic overgrowth was excised. The skin of the posterior portion of the pinna was reflected. The strip of fascia lata was now split lengthwise for one-third of its extent, and the two tongues so fashioned were sutured to the fascia and cartilage of the pinna, one anteriorly and the other posteriorly. The free end of the fascial strip was now burrowed under the scalp, and sufficient traction was exerted on it to bring the pinna up to a more nearly normal level (fig. 3 *B*). Two small holes were drilled through the outer table of the skull, and the fascia was then secured in its new position by threading fine steel wire through the holes. In addition, a number of black silk sutures were employed to bind the fascial strip to the external fascia of the temporal muscle (fig. 3 *C*). The scalp was closed in separate

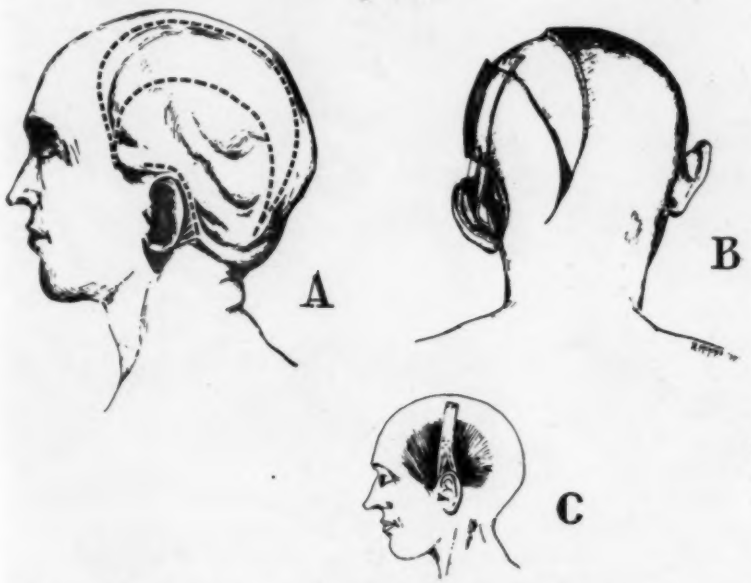

Fig. 3.—Operative procedure. The sketch at *A* indicates by broken lines the course of the scalp incisions. At *B* are illustrated the reflection of the skin from the posterior face of the pinna and the sites at which the two tongues of split fascia lata were sutured to the pinna. The free end of the fascial strip is shown beneath the scalp, secured to the vertex of the skull by steel wire sutures. At *C* are indicated black silk sutures binding the fascial strip to the external fascia of the temporal muscle.

layers, interrupted black silk sutures being used through the galea and skin. Five steel wire retention sutures were placed at regular intervals along the horseshoe-shaped incision. In anticipation of a serous or bloody ooze, a Penrose drain was led from under the superior margin of the scalp flap out through the incision in the postauricular region.

The gross specimens consisted of several large crescent-shaped strips of scalp varying from two to four times normal thickness. The outer surface of the skin appeared healthy. The galea was thin but otherwise normal in appearance. The

cut section revealed a dense, white, irregular pearly-appearing tissue which occupied the position normally represented by the areolar layer. Microscopically, this consisted of large bundles of fibrous tissue in which were arranged many mesodermal cellular elements in parallel formation. The cells varied in shape from fusiform fibroblasts to more primitive stellate mesenchymatous cells. In the low power magnification numerous whorl-like patterns were prominent. The fibrous bundles were solely of the collagenous type. No elastic fibers were seen,

Fig. 4.—Photomicrograph (hematoxylin and eosin stain; × 90) of a specimen of scalp obtained at operation in December 1938. The general pattern is characterized by sheaflike bundles and whorls of connective tissue. The usual features of malignancy are absent.. Fibroblastic elements predominate, ranging in type from spindle-shaped cells associated with much fibrous tissue to stellate mesenchymatous elements associated with a myxomatous matrix. Blood vessels are sparse and appear usually at the center of a whorl.

nor were there any epithelial elements. Between the adjacent capsules were scattered occasional round cells and plasma cells. In places, relatively clear blue areas representing a matrix of mucinous (myxomatoid) substance were visible (fig. 4). In certain sections fringed-out nerve fibrils and aberrant ganglion

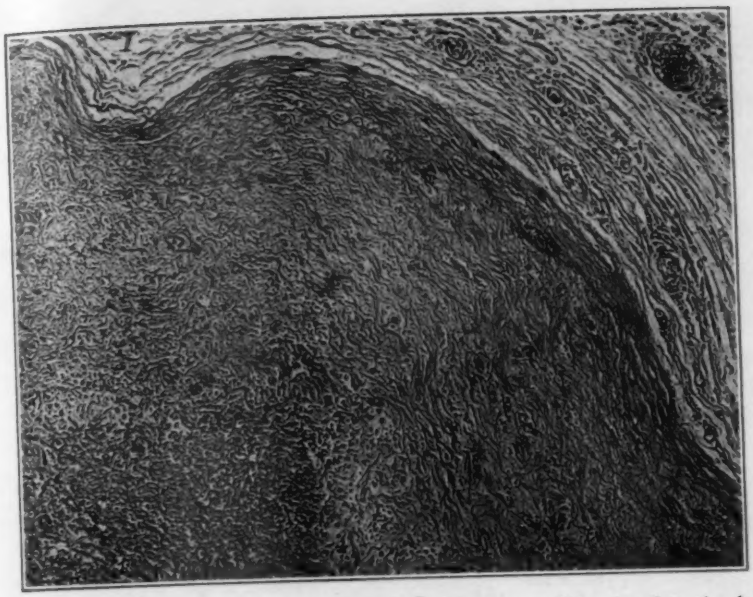

Fig. 5.—Photomicrograph (hematoxylin and eosin; × 50), showing the large nerve nodules which lent to the tumor its plexiform character.

Fig. 6.—Photomicrograph (Weigert stain; × 50), demonstrating the modified nerve tissue in the center of which there remain a few myelinated fibers. Marked proliferation of endoneurium and perineurium is visible within a loose connective tissue matrix.

cells were demonstrable within knots of dense connective tissue (fig. 5). This feature appears to justify interpretation of the tissue as belonging to the complex tumors of the neurofibromatous group.

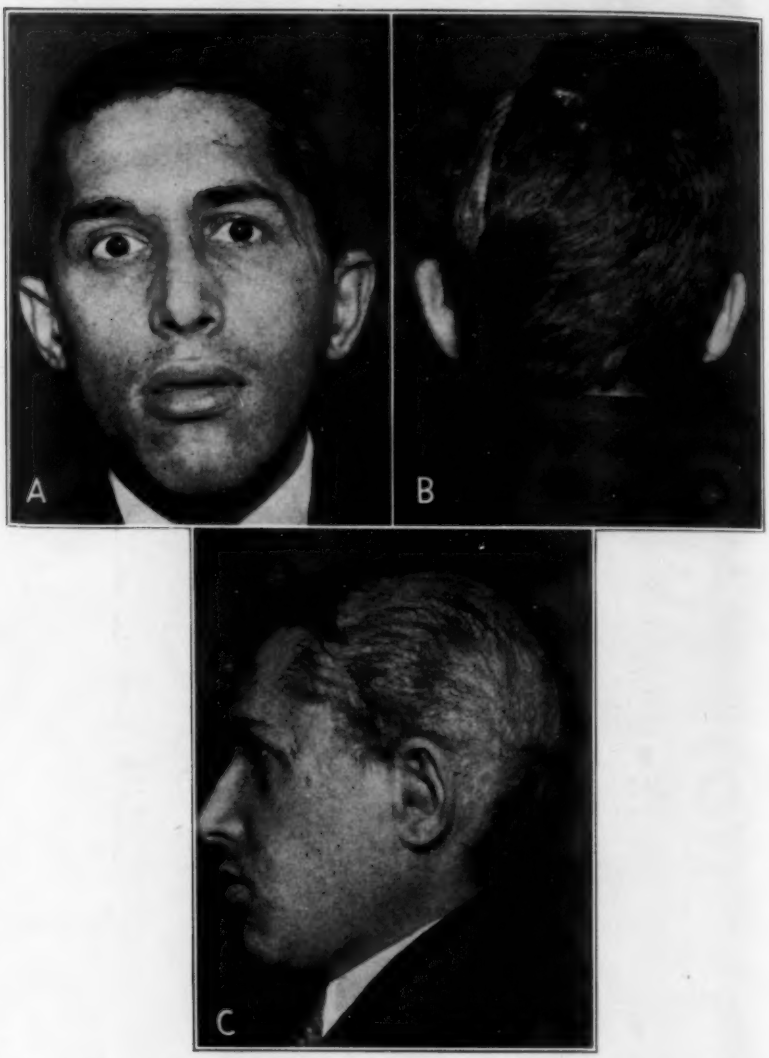

Fig. 7.—Photographs taken two months after operation. The elevated position of the left pinna is demonstrated. Its hypertrophy is apparent. The lines of the healed incisions in the scalp may be made out. The vigor of growth of the hair in the normal portion of the scalp may be compared with that in the affected area.

The postoperative course was fairly satisfactory. The Penrose drain was withdrawn on the fourth postoperative day. At this time the skin sutures were

also removed. The large circumlinear incision healed by first intention. The ears matched well in respect to their position on the head. Toward the end of the first week a serous discharge appeared in the region of the postauricular incision, and within a few days the edges of the skin here revealed an undue redness, so that it seemed indicated to open the more anterior portion of the postauricular incision. No definite pus was encountered, and the wound remained clean save for a mild saprophytic invasion. Wet dressings were applied, and healing by second intention was achieved during the next three weeks. By the middle of

Fig. 8.—Lateral view taken nine months after operation. No visible redundance of the scalp is apparent, and the ear is maintained approximately in the normal position.

December the hair was growing over the scalp, and the patient was discharged cosmetically improved (fig. 7). Close contact has been maintained with the patient since his discharge, and there have been no significant alterations in the plastic result during the ten months since operation. The most recent photograph (fig. 8) was made on Sept. 1, 1939. Palpation at present fails to disclose any increase in thickness of the scalp tissues, and the skin everywhere appears to be applied closely to the vault. The upper margin of the pinna remains at approximately the same level as that noted immediately after operation.

COMMENT

The present case represents a special type of so-called turban tumor. The generic significance of this term is of dubious value. Ronchese[1] attempted to limit its meaning to "nodular basal cell epithelioma of the scalp with cylindromatous degeneration." Other writers, however, have not conformed closely to this recommendation, the result of which is that the term connotes not a specific entity but merely a gross descriptive aspect of certain tumors of the scalp.

Although diffuse fibromatous tumors of the skin of the thighs, arms, trunk and buttocks (elephantoid tumors) are not uncommon, a careful inquiry into the literature of the past decade has failed to disclose a single recorded instance of tumor of the scalp which bears a close resemblance to that reported here. A number of standard works on plastic surgery, including those of Hunt[2] and Gillies,[3] have been consulted, but among these no comparable case is discoverable. MacCallum[4] described a case in which the histopathologic picture was similar but the clinical features were unlike those of the present case in that the tumor was rigid and formed a thick cap over the entire scalp. No mention was made of implication of the pinna by the growth. The only other recorded instance which even superficially resembles the present one was a case of mesenchymoma reported by Tauber, Goldmann and Barrett.[5] However, a tendency to ulceration and certain clearcut clinical and histologic evidences of malignancy permit a ready distinction between their case and that here reported. In his discussion of neurofibromatosis, Kaufmann[6] alludes to a case of elephantic plexiform neuroma in a girl aged 19. The clinical description, although meager, appears to resemble that of the present patient, and the microscopic pictures in the two cases are similar. In Kaufmann's case, however, the tumor was described as "growing rapidly toward the end."

Comparison of the histologic features of the specimen obtained in 1928 with that obtained in 1938 impresses one with the greater evidence of degeneration in the latter, viz., the more heterogeneous character of the fibrous matrix, the variability of cell types, the whorls and eddies

1. Ronchese, F.: Multiple Benign Epithelioma of the Scalp (Turban Tumors), Am. J. Cancer **18**:875, 1933.

2. Hunt, H. L.: Plastic Surgery of the Head, Face and Neck, Philadelphia, Lea & Febiger, 1926.

3. Gillies, H. D.: Plastic Surgery, London, Oxford University Press, 1920.

4. MacCallum, W. G.: A Textbook of Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 948.

5. Tauber, E. B.; Goldmann, L., and Barrett, C.: Mesenchymoma: A New Type of Turban Tumor, Arch. Dermat. & Syph. **37**:444 (March) 1938.

6. Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 3, p. 2025.

and the myxomatoid areas. Generally speaking, the ratio of fibrous to cellular elements is greater in the later specimen. It thus appears more "played out" than the early, more cellular fibroma. Observation of the patient during the ten months since operation affords some ground for the belief that the active growth of the scalp tumor may have reached a standstill. This circumstance may have obtained for some time prior to operation. Spontaneous cessation of growth is not, of course, an unusual feature of the life history of certain benign fibromatous tumors, the most notable illustration of which is provided by the common warts and pedunculated fibromas of the skin. Kaufmann [6] recorded the pertinent observation with reference to neurofibromatous tumors that "later the elephantiasis may become stationary." If this supposition should prove correct in the present case, the ultimate prognosis would be considerably improved in so far as the necessity for future surgical treatment is concerned.

The reason for such a "spontaneous" arrest of growth is not obvious, and it seems likely that the proper explanation will not be forthcoming until the present obscure understanding of the biology of normal growth and neoplastic processes has been clarified. The present paper is not the place for a detailed consideration of the problem, but the recent suggestion of Laidlaw [7] in this connection merits more than casual notice. This writer reconsidered the hypothesis of parasitic origin of certain neoplasms in the light of recent developments in virus research. He referred to the rather convincing experimental evidence of Rivers and Ward, Ledingham and Gye, Rous and Shope [8] that fibromas, sarcomas and myxomas can be regularly induced by the injection of viruses into animals of the avian and mammalian series. Not the least significant point of Laidlaw's discussion is the implication arising from the observation that antiserums possessing power of agglutinating and neutralizing the "tumor agent" may be demonstrated. On such an immunologic basis it is conceivable that neoplastic growth might eventually be brought to a halt. The notion is highly stimulating because of its wide pathogenic and therapeutic significance, and it deserves further experimental inquiry.

Concerning the classification of the present specimen as a neurofibroma, it must be conceded that, in view of the incomplete state of knowledge, this is somewhat arbitrary. It is by no means generally agreed that these tumors take their origin from neural elements. Some writers (Verocay; Durante) believe them to arise from Schwann sheath

7. Laidlaw, P. P.: Virus Diseases and Viruses, New York, The Macmillan Company, 1939, p. 36.

8. Shope, R. E.: Infectious Fibroma of Rabbits: Infection with Virus Myxomatosum of Rabbits Recovered from Fibroma, J. Exper. Med. **63**:43, 1936.

cells. Others (Wegelin) regard them as deriving from the endoneurial and perineurial connective tissues. Still another view (Harbitz) holds that these tumors result from developmental anomalies of connective tissue and are akin in all basic respects to fibromas, myxofibromas and sarcomas. Almost all writers agree with Durante and with Green and Bosanquet [9] that neurofibromas are prone to undergo metamorphoses, taking on the appearance of connective tissue, imbibing mucin and fat droplets and generally simulating the histologic characteristics of fibromas, myxomas and lipomas. The common embryologic parentage (mesenchyme) of these several tissues seems to account reasonably for the demonstrable mutations.

SUMMARY

An unusual instance of extensive plexiform neurofibromatosis of the scalp is reported. The clinical history is supplemented by two histologic specimens, the first taken soon after the neoplastic process was established and the second a decade later, when, seemingly, further growth had been either arrested or markedly retarded. The steps of the operative procedure employed to deal with the disfigurements incidental to the growth of the tumor are described. In essence, they consisted of fascial suspension of the dependent pinna and extensive resection of the redundant portion of the scalp.

9. Green, T. H.: Pathology and Morbid Anatomy, revised and enlarged by W. C. Bosanquet, ed. 10, Philadelphia, Lea Bros. & Co., 1905, p. 108.

LEIOMYOMA OF THE ROUND LIGAMENT

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AND
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Wells [1] is generally credited with being the first to report a case of leiomyoma of the round ligament. In 1865 he reported 2 cases of inguinal tumors which were described as "fibrous tumors of the round ligament;" one growth was the size of a small orange and the other the size of a coconut.

Sänger,[2] in 1883, found reports of 11 cases of tumor of the round ligament in the literature and added 1 of his own. In his case the tumor was a fibromyosarcoma. Emanuel,[3] in 1903, added 68 cases. Taussig,[4] in 1914, brought the total number of cases to 141.

Watkins,[5] in 1933, collected 173 cases of tumor of the round ligament from the literature; in 87 of these the tumor was a fibromyoma and was reported as a fibroma or a myoma. In 8 cases a diagnosis of sarcoma was made, and in all but 1 the sarcoma represented a malignant degeneration of a fibromyomatous growth.

Because of the inclusion of fibromas in the myomatous group, the exact number of leiomyomas which have been reported cannot be accurately ascertained. However, Horine,[6] in 1933, collected 36 cases of tumor of the round ligament which had been reported since publication of the article by Taussig in 1914. In 7 of these cases the tumor was a leiomyoma. In 1 case the growth was bilateral. Although a number of

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From the Division of Surgery, the Mayo Clinic.

1. Wells, S.: Fibrous Tumors of the Round Ligament of the Uterus, Brit. M. J. **2**:484, 1865.

2. Sänger, M.: Weitere Beiträge zur Lehre von den primären desmoiden Geschwülsten der Gebärmutterbänder, besonders der Ligamenta rotunda, Arch. f. Gynäk. **21**:279-308, 1883.

3. Emanuel, R.: Ueber Tumoren des Ligamentum rotundum uteri, Ztschr. f. Geburtsh. u. Gynäk. **48**:383-427, 1903.

4. Taussig, F. J.: Sarcoma of the Round Ligament of the Uterus, Surg., Gynec. & Obst. **19**:218-223 (Aug.) 1914.

5. Watkins, R. E.: Tumors of the Fallopian Tubes, Ligaments, and Pelvic Cellular Tissues, in Curtis, A. H.: Obstetrics and Gynecology, Philadelphia, W. B. Saunders Company, 1933, vol. 2, chap. 63, pp. 1041-1088.

6. Horine, C. F.: Tumors of the Round Ligament, Am. J. Obst. & Gynec. **25**: 446-448 (March) 1933.

cases of tumors of the round ligament have been reported since 1933, the only case of leiomyoma was that reported by Pardini [7] in 1934.

The largest leiomyomas have been those reported by Ward,[8] by Perewaloff [9] and by Craig.[10] In Ward's case the tumor extended intra-abdominally, above the umbilicus, measured 46 by 48 cm. and weighed 30 pounds (13.6 Kg.). In Perewaloff's case the tumor was situated in the labium majus; it hung to the knees and weighed 31 pounds (14.1 Kg.). However, the average diameter is usually given as approximately 5 cm.

In Emanuel's series, the right round ligament was involved three to four times as frequently as the left. Taussig, who after publication of Emanuel's report found 20 cases of tumor on the right side and 17 of tumor on the left side, doubted an actual preponderance for the right side. In our series of 11 cases of leiomyoma only 4 of the tumors were on the right side.

A leiomyoma may arise in any portion of the round ligament. Watkins found that in 69 per cent of the reported cases of tumor of the round ligament the growth was extra-abdominal. The fact that a superficial tumor is observed earlier and is more easily recognized than is a deep tumor may account for this greater frequency of extra-abdominal tumors of the round ligament. Only 3 of the leiomyomas in our series were extra-abdominal (see accompanying table). A tumor which arises in the intra-abdominal, or peritoneal, portion of the ligament may become pedunculated or may grow between the leaves of the broad ligament. One which arises near the internal inguinal ring may grow subperitoneally along the abdominal wall. A tumor which originates within the inguinal canal may project through either inguinal ring, and has been known to grow upward between the muscles of the abdominal wall. A growth which springs from the insertion of the round ligament in the labium majus appears as a tumor of the labium.

Leiomyoma of the round ligament produces no characteristic symptoms. A pedunculated tumor of the round ligament, like a similar tumor of the uterus, may become strangulated by torsion. An intra-abdominal tumor of the round ligament usually is indistinguishable on physical examination from a uterine leiomyoma or an ovarian tumor. One which is situated in the inguinal region or in the labia must be distinguished from hernia, from enlarged inguinal lymph nodes, from vari-

7. Pardini, I.: Un mioma della porzione intraddominale del ligamento rotondo, Clin. ostet. **36**:355-361 (June) 1934.

8. Ward, W.: Large Fibroid of the Round Ligament, Am. J. Obst. **77**:152, 1918.

9. Perewaloff, cited by Craig.[10]

10. Craig, R. G.: Tumors of the Round Ligament, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1928, vol. 11, chap. 21, pp. 1-8.

Clinical Data in Eleven Cases of Leiomyoma of the Round Ligament

Case	Age, Years	Marital State	Pregnancies	Children Born Alive	Symptoms	Site of Tumor: Round Ligament Involved	Site of Tumor: Portion of Ligament Involved	Size of Tumor	Associated Pelvic Disease	Clinical Diagnosis
1	43	M	1	1	Superficial abdominal tumor	Left	Inguinal	20 x 15 x 12 cm.	.....	Teratoma (?)
2	45	M	1	1	Occasional attacks of pain in right lower quadrant	Right	Intra-abdominal	2 mm. to 1.5 cm.	Adenomyoma of right round ligament; multiple pedunculated leiomyomas of uterus	Cyst of right ovary; fibroid uterus
3	32	M	1	1	None	Left	Intra-abdominal	8 x 7 x 7 cm.	.....	Subperitoneal fibroid or tumor of ovary
4	48	M	1	1	Moderate urinary frequency; soreness over bladder; pain in left hip	Left	Intra-abdominal	15 x 15 x 8 cm.	.....	Ovarian cyst
5	33	M	1	1	Dysmenorrhea; abdominal mass	Right	Intra-abdominal	7 cm.	.....	Uterine fibroid
6	42	S	0	0	Dysmenorrhea; mass in right lower quadrant	Left	Intra-abdominal	.....	Leiomyomas of uterus	Multiple leiomyomas of uterus
7	35	D	0	0	Pain and lump in right lower quadrant; lump became larger during menstrual periods	Left	Intra-abdominal	7 mm. to 4.5 cm.	Pedunculated uterine leiomyomas; chronic abscess	Endometriosis
8	49	M	4	3	Lump in right groin	Right	Inguinal	.....	.....	Omental hernia or cyst of round ligament
9	46	M	1	1	Dysmenorrhea; pain in right flank and back	Left	Intra-abdominal	2.5 cm.	Leiomyoma of left fallopian tube; purulent salpingitis on right side	Cyst of right ovary
10	37	M	1	0	Dull pain in right lower quadrant; sensation of incomplete micturition	Left	Intra-abdominal	2.5 cm.	Multiple leiomyomas of uterus	Multiple leiomyomas of uterus
11	35	M	9	8	Mass in right labium	Right	Labial	6 cm.	.....	Cyst of labium

cocele, from hydrocele of the canal of Nuck and from other tumors of the round ligament, namely, adenomyoma (Neel [11]), fibroma, lipoma, dermoid and sarcoma. In the labia one must also rule out the Bartholin cyst and adenoma hidradenoides.

Attention was attracted to leiomyoma of the round ligament by one of us (Mayo), who recently operated in a case in which the patient had a tumor of the round ligament unusual in both situation and size. It was the largest leiomyoma of the round ligament that has been encountered at the Mayo Clinic. This case and the 10 other cases in which a tumor of the round ligament has been removed surgically at the clinic form the basis of this report.

REPORT OF CASES

CASE 1.—A married woman aged 43 came to the clinic on May 3, 1939, because of a large superficial tumor on the lower part of the abdominal wall (fig. 1). The patient had been pregnant only once, and the child had been born alive. There was no family history of diabetes mellitus; the patient's father had had hypertension.

Albuminuria had been present since the birth of her child, sixteen years before she came to the clinic, and she had had edema of the ankles for several years. She had always been obese. Five years before she came to the clinic she had noticed that "waves appeared before her eyes" when she did close work. Examination at that time had disclosed that the value for her systolic blood pressure was 200 mm. of mercury. A diagnosis of hypertension had been made. Since then, her systolic blood pressure had varied between 160 and 180 mm. For a few weeks before she came to the clinic she had noticed that her vision for close work was worse than it had been previously.

In July 1935 she had noticed a mass about the size of a small lime in the left inguinal region. The mass had increased steadily in size and had extended toward the midline of the body. When the patient was first observed at the clinic the tumor was about 18 cm. in diameter and hung down over the symphysis pubis. It had never caused any pain, and the only discomfort it had caused was the result of its size, weight and situation. The patient had received conflicting opinions regarding the advisability of surgical removal of the tumor.

The patient was 62⅛ inches (157.8 cm.) in height and weighed 193 pounds (87.5 Kg.). The systolic blood pressure was 280 mm. of mercury, and the diastolic pressure was 156 mm. The heart sounds, especially the aortic, were accentuated. The abdomen was large. A round mass about 18 cm. in diameter was found in the lower part of the midline of the abdomen. The mass was attached to the left inguinal, labial and suprapubic regions by a broad pedicle. The mass did not transmit light. The uterus was of normal size. Examination also disclosed a cystocele, grade 2, and edema of the ankles, grade 1.

Examination of the ocular fundi disclosed narrowing, grade 1, and chronic hypertensive sclerosis, grade 1, of the retinal arteries. In a few scattered regions there were a postspastic type of uneven narrowing, grade 2, and small hemorrhages. There were a few "cotton-wool" exudates, which were undergoing absorption, and one large fresh exudate was found above the optic disk of the left eye.

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11. Neel, H. B.: Adenomyoma of the Inguinal Region: Report of Three Cases, Surgery **2**:769-779 (Nov.) 1937.

Urinalysis disclosed albuminuria, grade 2, glycosuria (the concentration of sugar in the urine was 1.48 per cent) and a few hyaline and granular casts. Routine examination of the blood did not disclose any abnormality. Three hours after the patient had had breakfast the concentration of blood sugar was 240 mg. per hundred cubic centimeters.

Roentgen examination of the thorax did not disclose any abnormality. An electrocardiogram revealed left ventricular preponderance and diphasic T waves in derivation I.

The clinical diagnosis was: (1) a superficial tumor in the lower part of the abdomen (possibly a teratoma), (2) hypertension, grade 3, (3) obesity and (4) diabetes mellitus.

The diabetes was controlled by a dietary regimen. Operation was performed on May 8. Regional anesthesia was used to supplement the anesthesia produced

Fig. 1 (case 1).—Tumor overhanging the symphysis pubis with a portion of its pedicle arising from the left inguinal region.

by the intravenous injection of pentothal sodium (sodium ethyl 1-methyl butyl thiobarbituric acid). An almost transverse elliptic incision was made across the tumor, which was well encapsulated and enveloped by superficial fascia. It seemed to be attached to the left round ligament and protruded through the left inguinal region as though it were a hernial sac. The peritoneal cavity was opened, and the round ligament was followed down to its uterine attachment. The tumor and adjacent portion of the round ligament were removed around the stump, the round ligament was brought to the pubic tubercle, the peritoneum was closed and the operation was completed as a left inguinal hernioplasty.

A cross section of the gross specimen had the typical appearance of a large leiomyoma which was undergoing degeneration in some places (fig. 2). The pathologic report was as follows: "Degenerating leiomyoma (fig. 3), 20 by 15 by 12 cm., intimately attached to the left round ligament. Weight, 1,900 Gm."

Fig. 2.—Cross section of the gross specimen in case 1.

Fig. 3.—Photomicrograph of the tumor in case 1, showing smooth muscle, cells and edema, × 185.

The patient made an uneventful recovery and was dismissed from the hospital in good condition on May 24. While she was confined to bed after the operation the systolic blood pressure was 175 mm. and the diastolic pressure was 98 mm.

CASE 2.—A married woman aged 45 complained of nervousness which had been present for many years and had been associated with occasional attacks of pain in the right lower quadrant of the abdomen. She had been pregnant only once and had given birth to a living child. Palpation revealed tenderness, grade 2, deep in the right lower quadrant of the abdomen. Pelvic examination disclosed what was thought to be a large cyst of the right ovary. A small nodule also was palpated above, and to the right of, the cervix. Operation disclosed multiple pedunculated uterine fibroids. The largest fibroid was 9 cm. in diameter. An adenoma 3 cm. in diameter was found in the right round ligament, about 5 cm. from the uterus. Multiple leiomyomas also were present in the right round ligament. The diameter of the largest of these tumors was 1.5 cm., and that of the smallest was 2 mm.

CASE 3.—A married woman aged 32 came to the clinic because of indigestion (which proved to be functional) and because of a pelvic tumor which never had caused any symptoms but had been discovered by her physician one week previously. She had been pregnant only once and had given birth to a living child. Pelvic examination disclosed a firm nodular tumor on the left side. It was thought to be a subperitoneal fibroid or an ovarian tumor. Operation disclosed that the tumor had arisen from the round ligament but was situated almost entirely within the broad ligament. A myomectomy with removal of a portion of the round ligament, 3 cm. long, was performed. The tumor, which was a leiomyoma, measured 8 by 7 by 7 cm. and weighed 120 Gm.

CASE 4.—The patient was a married woman aged 48 who had been pregnant only once and had given birth to a living child. She came to the clinic because of moderate frequency of urination and soreness over the bladder, which had been present for nine months, and because of pain in the left hip, which had occurred occasionally during the previous two years. She was very obese, and her abdomen was pendulous. Palpation revealed slight tenderness over the bladder. Pelvic examination disclosed a soft, flabby cyst on the left side. The cyst reached almost to the umbilicus and was thought to be an ovarian cyst. Operation disclosed a cystic tumor which was attached to the left round ligament by a twisted pedicle. The tumor measured 15 by 15 by 8 cm. and weighed 675 Gm. It was an edematous, subserous, pedunculated leiomyoma. Removal of the tumor relieved the symptoms.

CASE 5.—The patient was a married woman aged 33 who had been pregnant only once and had given birth to a living child. She complained of menstrual pain situated in the lower part of the right side of the abdomen. The pain had occurred since puberty and had increased in severity. It had come on after the onset of the menstrual flow and had incapacitated her for three days each month. Her menstrual periods had been regular. Two years before she came to the clinic she had noticed a lump in the lower part of the abdomen. Pelvic examination at the clinic disclosed a tumor on the right side. The tumor was thought to be a uterine fibroid. Operation disclosed an intraligamentous leiomyoma which had arisen from the round ligament. The tumor was 7 cm. in diameter; it was adherent to the right fallopian tube, the right ovary and the omentum. The right fallopian tube and the right ovary were removed with the tumor. The appendix also was removed. Since the operation, the dysmenorrhea has disappeared and the patient has given birth to two children.

CASE 6.—A single woman aged 42 came to the clinic because she had noticed a mass in the right lower quadrant of the abdomen three weeks previously. Since puberty she had had menstrual pain in the right lower quadrant of the abdomen, and she had noticed some blood clots during her menstrual periods. "Gas pains" in the right lower quadrant of the abdomen had been present for eight years, and she occasionally had noticed spots of blood midway between her menstrual periods, which always had been regular. Abdominal and pelvic examination disclosed a large, hard, irregular tumor which filled the pelvis. The preoperative diagnosis was multiple leiomyoma of the uterus. Operation confirmed the diagnosis. The diameter of the individual tumors varied from 1.5 to 8 cm. The uterus, tubes and ovaries were removed. A myomectomy also was performed for a leiomyoma of the left round ligament. The size of this tumor was not mentioned.

CASE 7.—A divorced woman aged 35 had never been able to become pregnant in seven years of married life. In 1924 an adenomyoma of the right round ligament and a draining sinus had been removed at the clinic. She had always had a slight pain in the right lower quadrant of the abdomen at the beginning of menstruation. In 1935 she came to the clinic complaining of severe pain which had been present in the right lower quadrant of the abdomen since the onset of menstruation, a week previously. She also had noted a lump in the right lower quadrant. This lump had enlarged during menstruation. On examination, motion of the cervix caused pain. The uterus was tipped to the right, and several small nodules were felt on it. It was thought that she probably had endometriosis. At operation, on Dec. 10, 1935, a congenital anomaly was found. There was no evidence of a fallopian tube on either side, and the only ovarian tissue found was situated high on the left lateral wall of the pelvis, extended downward and was incorporated in the round ligament, which was inserted in the wall of the uterus at a point about opposite the uterine artery. Along this ligament were situated three or four leiomyomas, which varied from 7 mm. to 4.5 cm. in diameter. A pedunculated fibroid was found in the left lateral wall of the uterus. The uterus and cecum were densely attached to a nodule in the right abdominal wall which proved to be a chronic abscess.

CASE 8.—The patient was a married woman aged 49 who had been pregnant four times and had given birth to three living children. A month before she came to the clinic she accidentally had discovered a hard lump in her right groin. The lump had not caused any symptoms. The patient recently had missed two menstrual periods, but this was attributable to her age. Examination revealed an oval cystic mass on the right side of the mons. The mass could not be reduced. It was thought to be a right, indirect omental hernia or possibly a cyst of the round ligament or its coverings. Operation revealed a leiomyoma of the right round ligament.

CASE 9.—The patient was a married woman aged 46. She had been pregnant only once but had not given birth to a living child. For three years before she came to the clinic she had had recurrent attacks of pressure-like pain in the right loin, flank and back. She also had had mild dysmenorrhea. Her menstrual periods were still regular, but the menstrual flow had become scanty during the six months before she came to the clinic. Pelvic examination revealed what was thought to be a cyst of the right ovary, which was the size of a peach. Operation disclosed a pedunculated leiomyoma of the left round ligament and a leiomyoma of the mid-portion of the left fallopian tube. The diameter of the tumor of the round ligament was 2.5 cm., and that of the tumor of the fallopian tube was 4 mm. Purulent salpingitis was present on the right side. The right tube measured 7 by 2 cm. Both of the tumors were excised, and the right fallopian tube and right ovary were removed.

CASE 10.—The patient was a married Negress aged 37, who had been pregnant once but had not given birth to a living child. A diagnosis of uterine tumor had been made two years before the patient came to the clinic. She recently had missed two menstrual periods, had had a dull pain in the right lower quadrant of the abdomen and had had a sensation of incomplete micturition. Palpation revealed a pelvic mass which extended upward as far as the umbilicus. The mass was thought to consist of uterine leiomyomas. A total hysterectomy was performed through the abdominal wall. The mass was found to consist of multiple intramural leiomyomas. The patient also had a leiomyoma of the left round ligament; this tumor was 2.5 cm. in diameter.

CASE 11.—The patient was a married woman aged 35 who had been pregnant nine times and had given birth to eight living children. A mass had developed in the right labium during the three years before she came to the clinic. It was thought to be a cyst of the labium. The mass, which was 6 cm. in diameter, was excised. It was first reported to be a myxofibroma, but further study disclosed that it was a leiomyoma which probably had arisen from the round ligament.

SUMMARY

Leiomyoma of the round ligament has been encountered surgically at the clinic in 11 cases, in which the patients were women between the ages of 32 and 49 years. Ten of the women were married; 9 had been pregnant, and 7 had given birth to living children. The tumors varied in size from 2 mm. in diameter to 20 by 12 by 15 cm. In 7 cases the growth was situated on the left side, and in 4 cases it was on the right side. In 2 cases it was multiple. In 8 cases the tumor was situated intra-abdominally in the peritoneal portion of the round ligament. In 2 of these cases the tumor was pedunculated, and in 2 other cases it was situated almost entirely within the broad ligament. In 3 cases the tumor was extra-abdominal; in 2 of these cases it was situated in the inguinal canal, and in the third case it was situated in the labium. A uterine leiomyoma was present in 4 cases. In 1 case there was also a myoma of the fallopian tube on the same side, and in another case multiple leiomyomas were associated with an adenomyoma of the round ligament.

In only 2 cases were there symptoms attributable to the tumor of the round ligament. Soreness of the bladder, frequency of urination and pain in the hip were present in 1 case, and severe dysmenorrhea was present in the other case. In both cases removal of the tumor was followed by disappearance of the symptoms. In 5 cases the symptoms were accounted for by other pelvic disease, and in 4 cases there were no symptoms aside from the presence of the tumor.

In none of these cases was the diagnosis made or suspected clinically. As has been stated, the diagnosis cannot be made if the tumor is intra-abdominal. However, one should suspect a leiomyoma of the round ligament in any case in which a woman of the child-bearing age has a tumor which arises from the inguinal or labial region if the presence of a hernia or of other, more easily recognized tumors has been excluded.

ECTOPIC PREGNANCY

ITS RELATION TO THE DIAGNOSTIC PROBLEMS OF THE GENERAL SURGEON

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The study of symptoms of ectopic pregnancy, augmented in this paper by observation of 81 patients treated surgically in the Ravenswood Hospital, Chicago, reveals results interesting not only to the gynecologist but to the surgeon, who faces the problem of differentiating "surgical" from "gynecologic" diseases of the lower part of the abdomen. Laboratory data which make the diagnosis almost specific, such as the Aschheim-Zondek reaction, are not always available, but once the possibility of an ectopic pregnancy is considered, these tests facilitate a more definite diagnosis. Although, as will be explained later, the blood counts are often bare of any diagnostic significance, there will be occasions when the patient's pallor and other manifestations of shock will make a diagnosis of internal hemorrhage definite. The only difficulty will be in determining the source of the hemorrhage; abnormalities in the menstrual history together with other manifestations, to be mentioned later, should lead one to the correct diagnosis.

PROBLEMS OF PREOPERATIVE DIAGNOSIS

All authors who discuss the diagnosis of ectopic pregnancy agree that in many instances it is made with difficulty because of the variations in the symptoms which are known to be present in this disease. The clearcut examples, with the typical textbook manifestations, are easily recognizable. But the percentage of misdiagnoses is still too large. The physician who must make his decision from bedside examination only may often face a difficult problem, and in many cases the correct diagnosis is impossible because of the general and vague symptoms. When symptoms of a severe hemorrhage are unequivocal and there is time for an Aschheim-Zondek test, a definite diagnosis is obviously possible.

Scheffey, Morgan and Stimson[1] stated: "Even today, the enigma of ectopic pregnancy . . . confronts us as a diagnostic problem." The

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1. Scheffey, L. C.; Morgan, T. R., and Stimson, C. M.: An Analysis of a Series of Eighty-Two Cases of Ectopic Pregnancy, Am. J. Obst. & Gynec. **24**: 103-115, 1932.

correct diagnosis was made in 78.8 per cent of their cases before the operation.

Urdan,[2] in his critical study of 474 cases, learned that the absolute diagnosis of ectopic pregnancy, except in the "tragic cases," is a difficult matter. The preoperative diagnosis was correct in 58.17 per cent of his series of cases.

Fitzgerald and Brewer [3] found 60.4 per cent of ectopic pregnancies correctly diagnosed; Jonas,[4] 73.3 per cent. These are percentages which have no bearing on the skill of the diagnostician but are an integral feature of the problem. A study of these reports also shows that there is a likelihood of diagnosing an ectopic pregnancy as some pathologic condition far removed from the pelvis.

Bubis [5] maintained that early diagnosis is difficult. He stated that "in many cases of typical textbook symptoms I found no extra-uterine pregnancy." Urden stated, "The knowledge of ectopic pregnancy is complete but the diagnosis is still a difficult problem."

According to Jonas,[4] "A typical case of extra-uterine pregnancy is unmistakable; yet an atypical case, even after rupture, may deceive the most astute clinician." This author also admitted that the diagnosis is easiest when the symptoms are acute and that the general symptoms of pregnancy are often missing; his patients were admitted to the hospital as ill women and not as pregnant ones! Scheffey, Morgan and Stimson [1] found the concomitant signs of pregnancy infrequent. Fitzgerald and Brewer [3] maintained that because of the obscurity of the diagnosis, the patients not infrequently go to a medical or a surgical service. They observed that 10.2 per cent of patients were operated on with the definite diagnosis of an inflammatory disease, 10.6 per cent with a diagnosis of either ectopic pregnancy or an inflammatory process, and 4.6 per cent with an indefinite diagnosis of a "surgical" condition of the abdomen; this represents an error of 25.4 per cent.

Experiences of this character always maintain the surgeon's interest in the diagnosis of ectopic pregnancy, and this clinical entity, as such, remains within that professional area in which the surgeon's realm intrudes on the influential sphere of the gynecologist. Therefore, this paper is an attempt to scrutinize the diagnostic value of the symptoms

2. Urdan, B. E.: Ectopic Pregnancy, Am. J. Obst. & Gynec. **20**:355-372, 1930.

3. Fitzgerald, J. E., and Brewer, J. I.: Extra-Uterine Pregnancy, Am. J. Obst. & Gynec. **30**:264-269, 1935.

4. Jonas, A. F., Jr.: An Evaluation of Signs and Symptoms in the Diagnosis of Extra-Uterine Pregnancy, New England J. Med. **209**:1324-1328, 1933.

5. Bubis, J. L.: Report on Seventy-Six Cases of Ectopic Gestation, Am. J. Obst. & Gynec. **17**:74-78, 1929.

which occur in ectopic pregnancy with particular reference to features which may lead to confusion with conditions in the field of general surgery.

ONSET

The time at which ectopic pregnancy ceases to be only a pathologic entity and becomes also a clinical entity is usually characterized by the appearance of pain and a retrospective history of irregular menstrual bleeding. The early symptoms of ectopic pregnancy either are severe and sudden or develop gradually over a period of several days or weeks. The reports of the different authors agree closely in this respect. Sudden onset of symptoms, especially of pain, prevails in frequency over gradual development of discomfort. Falk and Rosenbloom [6] noted a sudden onset in 65.2 per cent, Jonas in 66.6 per cent and Fitzgerald and Brewer in nearly two thirds of all cases.

TABLE 1.—*Ectopic Pregnancy*

	Number of Cases	Frequency in Percentage
1. Pain:		
a. Sudden onset of severe pain in lower part of abdomen (indicating rupture of pregnant organ)	61	80.3
b. Gradually developing pain a long time before rupture (indicating the presence of a space-occupying process causing pressure)	12	15.8
c. No pain	3	3.9
Total	76	100.0
2. Fainting	13	16.0
3. Nausea and vomiting	29	35.8

SIGNS AND SYMPTOMS

In 80.3 per cent of cases (table 1) the patient was seized with sudden pain on one side of the lower part of the abdomen that caused a momentary disability. This pain indicates rupture of the pregnant organ and the peritoneal shock due to laceration of the peritoneal surface of the tube and consequent hemorrhage into the peritoneal cavity. Sudden symptoms, such as shock, collapse and unconsciousness, appear, according to Bubis' experience, only when sudden massive hemorrhage occurs. In a smaller group of patients (15.8 per cent) the pain developed gradually, probably as a pressure symptom elicited by the space-consuming growth of the pregnant organ or by a slowly growing hematoma. Often the patient says she has had moderate pain and discomfort in the lower part of the abdomen for a number of days or weeks before the sudden

6. Falk, H. C., and Rosenbloom, M. A.: Extra-Uterine Pregnancy: Analysis of Three Hundred and Thirteen Cases from Harlem Hospital, Surg., Gynec. & Obst. **62**:228-235, 1936.

onset of severe pain. In some patients the prodromal symptoms disappear for days. Jonas found that severe pain with sudden onset is preceded by hours to weeks by inconstant colicky pain in the lower part of the abdomen. According to this author, pain often loses its greatest intensity within half an hour, continuing less severely thereafter.

Pain.—This is the most common symptom of ectopic pregnancy; it is present according to Jonas in 97.7 per cent of cases and according to Fitzgerald and Brewer in 96.4 per cent. My series presented a frequency of 96.1 per cent. Curtis [7] explained the pain caused by rupture of a pregnant tube by tension of the peritoneum, its tearing and pressure of the extravasated blood on the peritoneum. He accounted for the pain associated with tubal abortion by distention of the tube, muscular contractions of the tube and pressure of the extravasated blood. In evaluation of pain as a diagnostic feature of ectopic pregnancy, three points must be considered: the type, the localization and the course of its intensity.

The pains as described by the patients with ectopic pregnancy may differ as may any other symptom of this disease. They are usually characterized as sharp cramps, stabbing pains, bearing down pains, labor-like pains, dull pains, gas pains, backache, pain in the bladder or rectal tenesmus. The latter two types of pain are noted particularly during micturition and defecation respectively. Jonas observed 20 cases of vesical discomfort and 13 of rectal tenesmus.

During the period preceding the rupture the pain is dull. Sudden, stabbing pain is the sign of perforation of the tube.

The site of the pain may vary greatly. This fact is invaluable, because it may direct one's attention to an accurate diagnosis. Therefore, a question pertaining to it should be asked the patient, since later the painful area increases in size and frequently comprises the whole lower half of the abdomen or more. However, Fitzgerald and Brewer stated that in their series localization of pain was not of great help either in diagnosing extrauterine pregnancy or in determining its site. Probably these authors had in mind the later spreading of the pain. Tenney [8] observed pelvic tenderness in 92 per cent of cases. Pain may occur all over the abdomen, in any of the four abdominal quadrants or only in the lower part of the abdomen. It may also occur (though rarely) as an epigastric pain or a pain in the shoulder. In a study of 474 cases Urdan [2] mentioned 28 patients who had pain in one or both shoulders. Pain is therefore located most frequently in the lower part of the

7. Curtis, A. H.: Obstetrics and Gynecology, Philadelphia, W. B. Saunders Company, 1933.

8. Tenney, B.: A Clinical and Pathological Study of One Hundred and Fifty Cases of Ectopic Pregnancy, New England J. Med. **214**:774-776, 1936.

abdomen. The frequency reported by Tenney [8] was 93 per cent; that reported by Fitzgerald and Brewer,[3] 52.6 per cent.

A confusing influence can be brought into the sometimes already complicated diagnostic picture by the change in severity of the pain. At the time of rupture it begins primarily as a sharp, agonizing and disabling pain in the lower part of the abdomen, but, as has been said, it may disappear as quickly as it came and leave the patient with only a slight dull pain, which in many cases comes back hours or days later with changing intensity.

Fainting.—Attacks of fainting were present in 16 per cent of my cases. This frequency comes close to that reported by some other authors: Falk and Rosenbloom observed fainting in 18.8 per cent; Jonas, in 13.3 per cent. Bubis encountered shock in 15.8 per cent; Scheffey, Morgan and Stimson, in 14.6 per cent. The last-mentioned authors observed syncope in 26.7 per cent. Fitzgerald and Brewer observed collapse in 18.2 per cent and fainting in 29 per cent of their cases; Urdan noted fainting in 28.91 per cent of his.

Nausea and Vomiting.—These symptoms were observed by Falk and Rosenbloom in 42.8 per cent and by Fitzgerald and Brewer in 37.4 per cent of cases. In the Ravenswood Hospital series the percentage was 35.8. This frequency of nausea and vomiting is obviously an obstacle to strict differentiation of ectopic pregnancy from other abdominal diseases. Scheffey, Morgan and Stimson observed this symptom in only 5 per cent of their cases, but they recorded it only when it was present at the time of admission to the hospital and omitted it from the statistics when it occurred at an earlier time.

Irregular Uterine Hemorrhage.—This is a frequent symptom. It occurred in 73.5 per cent of the group studied by Falk and Rosenbloom. Bubis noted it in 51 per cent, and Jonas' group reached the peak with 90 per cent. In the total group described by the last-mentioned author, 60 per cent of the patients had missed one or more menstrual periods. Scheffey, Morgan and Stimson counted 64.6 per cent of cases in which irregular bleeding occurred.

Tenney classified cases of irregularity of the menstrual cycle associated with ectopic pregnancy into the following groups: 45 per cent, one period missed; 52 per cent, one or more periods missed; 70 per cent, one or more periods missed or very scanty menstruation, and 82 per cent, irregular bleeding. He stated that the absence of bleeding indicates a living embryo, with which rupture is more dangerous.

Fitzgerald and Brewer reported the following data: More than 33.3 per cent of patients did not miss a menstrual period; 11.4 per cent had bleeding which began as menstrual bleeding at a regular time but continued longer than a normal period; 12.8 per cent had the

normal period replaced by a diminished or intermittent flow ("spotting"); only 17.6 per cent had no bleeding during the ectopic pregnancy; 30 patients had symptoms before they missed a menstrual period; 58 patients missed periods but had no subsequent bleeding; 17.6 per cent had no bleeding between the time of the last period and the time at which the diagnosis was made; 50.6 per cent had only spotting following normal menses; 6.4 per cent had spotting for only one day; 20.6 per cent had moderate bleeding, and 8.2 per cent had profuse bleeding.

Urdan stressed the combination of irregular hemorrhage with pain in 89.83 per cent of his patients, because hemorrhage alone occurred only in 2.77 per cent of his cases and pain alone in 7.3 per cent. He also noted that the hemorrhages associated with ectopic pregnancy are of lesser intensity than those associated with threatened abortion.

TABLE 2.—*Vaginal Hemorrhages in Ectopic Pregnancy*

	Number of Cases	Frequency in Percentage
1. Irregular hemorrhages of any kind during the interval between the last regular menstruation and the time of operation	48	70.6
2. At least 1 menstruation missed, but no irregular hemorrhage from the last menstruation to the time of operation	14	20.6
3. No regular menstruation missed before the operation and no irregular hemorrhage (i. e., before the next expected regular menstruation)	6	8.8
Total	68	100.0
Hemorrhage started with onset of pain	14	20.6

Falk and Rosenbloom observed irregular hemorrhages in 73.5 per cent of their cases, but in 14 per cent the acute symptoms began before the onset of the next expected regular period. Bubis recorded a 51 per cent incidence of irregular hemorrhages; Jonas found that 90 per cent of his patients had had vaginal bleeding at one time or another and that 60 per cent had missed one or two periods. In Scheffey, Morgan and Stimson's group the incidence was 64.6 per cent; Thiemeyer's [9] group had an incidence of 85.2 per cent of vaginal hemorrhages, and only 11.8 per cent of his patients had no vaginal bleeding.

In the Ravenswood Hospital series, irregular hemorrhages occurred in 70.6 per cent (table 2). They varied in duration and quantity from case to case. The cases could be grouped in gradual steps from those in which there were occasional vaginal hemorrhages up to those in which there occurred frequent, even daily, ones. In some cases the hemorrhages were described by the patients as slight spotting; in others, as profuse bleeding.

9. Thiemeyer, A. C.: The Diagnosis of Ectopic Pregnancy, M. Rec. **142**: 373-375, 1935.

The cases in which there were no irregular hemorrhages amounted to 29.4 per cent. They can be divided into two groups. In the first (20.6 per cent) at least one menstrual period was missed; in the second (8.8 per cent), no regular menstruation was missed.

These statistical figures concerning the uterine hemorrhages associated with ectopic pregnancy indicate that in taking the history of a woman with abdominal symptoms special diligence should be exercised in discussing this subject in all its details with the patient, even though the tentative diagnosis may be acute appendicitis. One should also keep in mind that, in contrast to normal pregnancies, the overwhelming majority of ectopic pregnancies are associated with irregular hemorrhage.

The eliminated blood should be examined for particles of tissue. The presence of decidual particles with complete absence of fetal villi speaks for an ectopic pregnancy; the presence of both decidual particles and fetal villi, for the abortion of a uterine pregnancy.

Blood Picture.—The diagnostic value of changes in the blood in cases of ectopic pregnancy depends on the amount of blood lost and the rate of hemorrhage above a certain minimum which is able to cause any significant change in the blood. From the standpoint of the surgeon, only a few important facts have to be kept in mind. Immediately after a hemorrhage there is no apprehensible change. Several hours is required after the loss of a certain amount of blood for replacement of the blood by body fluids, which causes dilution of the blood and hence a decrease in the red blood count. When no further hemorrhage takes place, the red blood corpuscles are replaced at the daily rate of about 50,000 to 80,000 per cubic millimeter. The hemoglobin content of the blood reaches its normal level much later than does the erythrocyte count. Within one or two hours after the hemorrhage, neutrophilic leukocytosis appears, in accordance with the general rule that leukocytosis follows hemorrhage in which the blood remains in a serous cavity, such as the peritoneal or pleural cavity, the subdural space or a joint cavity. Leukocytosis decreases at a rate comparable to the rate of absorption of the extravasated blood. Farrar [10] divided her 150 patients with ectopic pregnancy into three groups, with leukocyte counts of 4,500 to 10,000, 10,000 to 16,000 and 16,000 to 36,350 respectively. Of the first group, rupture occurred in 59.7 per cent. Of the third group, in which there was the highest leukocyte count, 100 per cent had either rupture or a tubal abortion. This study demonstrates that the white blood cell count fluctuates as a function of the phases of the hemorrhage.

It cannot be emphasized too strongly that changes in the blood picture occur after a relatively large loss of blood but that hemorrhage

10. Farrar, L. K. P.: The Value of the Leucocyte Count as an Aid to the Diagnosis in Ectopic Gestation, Surg., Gynec. & Obst. **41**:655-663, 1925.

below a certain minimum will not cause any appreciable change in the blood count. Therefore, in the presence of a normal blood count it is not justifiable to rule out ectopic pregnancy.

Site of Ectopic Pregnancy.—One cannot escape the impression that ectopic pregnancy occurs more frequently on the right side than on the left, as may be seen from table 3, computed from the findings of other authors and confirmed also by my series. Only the series reported by Scheffey, Morgan and Stimson is an exception to this rule.

In the Ravenswood Hospital group it was found that 61.3 per cent (table 4) of the recorded cases were instances of ectopic pregnancy of

TABLE 3.—*Sites of Ectopic Pregnancy Mentioned by Other Authors*

	Bubis[5]	Jonas[4]	Scheffey, Morgan and Stimson[1]	Thiemeyer[9]	Urdan[2]
Right tube	45	48	39	56	227
Left tube	31	26	43	48	187
Right ovary	2				
Left ovary	0				
Abdominal pregnancy	1				
Omental pregnancy	1				
Left tube (lithopedion)	1				
Site unknown	1				

TABLE 4.—*Sites of Ectopic Pregnancy in the Ravenswood Hospital Series*

	Number of Cases	Frequency in Percentage
1. Right tube	49	61.3
2. Left tube	29	36.2
3. Ovary (left, 1 case; right, 1 case)	2	2.5
Total	80	100.0
4. Recurrent tubal pregnancy	4	5.0

the right tube. The left tube was the site of the ectopic pregnancy in only 36.2 per cent. Ovarian pregnancies had a frequency of 2.5 per cent. Ectopic pregnancy may occur more than once during the life of a patient, as can be seen from the 5 per cent of cases in which operation had been performed a second time for ectopic pregnancy. Jonas mentioned 2 cases (2.2 per cent) and Fitzgerald and Brewer 13 cases (2.6 per cent) of repeated ectopic pregnancy.

Bilateral ectopic pregnancy occurring simultaneously is an extremely rare finding. Johnson and Diasio [11] operated in 1 case of bilateral tubal pregnancy and collected 10 other cases from the literature.

11. Johnson, H. H., and Diasio, J. S.: Bilateral Tubal Pregnancy with Rupture of Both Tubes, Am. J. Obst. & Gynec. **17**:116-117, 1929.

Cullen's Sign.—Bluish discoloration of the umbilicus in the presence of free blood in the peritoneal cavity was not observed as frequently as one would expect. Bubis, one of the few authors who looked for this symptom, found it only in 3 of 76 cases. Jonas emphasized the fact that he had never observed this symptom.

Type of Intra-Abdominal Hemorrhage.—It is of interest to add to this statistical study a summary of the different types of intra-abdominal hemorrhage found at the time of operation (table 5). The most frequent type was rupture of the tube into the free peritoneal cavity, the blood accumulating in variable amounts within the cavity (73.2 per cent). In 11.3 per cent of the recorded cases there was hemorrhage only from the fimbriated end of the tube with no rupture of the tube itself. The pregnant tube may rupture also into the broad ligament and form a hematoma in its loose connective tissue (2.8 per cent). Rupture of a pregnant ovary occurred in both instances of ovarian

TABLE 5.—*Type of Intra-Abdominal Hemorrhage*

	Number of Cases	Frequency in Percentage
1. Rupture of tube and hemorrhage into peritoneal cavity	52	73.2
2. Hemorrhage from fimbria into peritoneal cavity	8	11.3
3. Not ruptured before operation	7	9.9
4. Rupture of tube and hemorrhage into broad ligament	2	2.8
5. Rupture of pregnant ovary	2	2.8
Total	71	100.0

pregnancy recorded in this paper, a frequency of 2.8 per cent of the total group of ectopic pregnancies.

The number of cases in which free blood was found in the peritoneal cavity is larger than that in which the tubes were perforated, because cases of tubal abortions and also cases in which there was an extravasation of blood into the tubal lumen, either by separation of the placenta or by erosion of a vessel, must be included.

Free blood in the peritoneal cavity was found by Scheffey, Morgan and Stimson in two thirds of all their cases.

The percentage of cases in which the diagnosis was made before the onset of acute symptoms and in which the pregnant tube was found still intact at the time of the operation was as high as 9.9.

Local Physical Findings.—The value of the diagnostic aid obtained by inspection, external palpation and bimanual vaginal examination of the pelvic organs differs from case to case. The constitution of slender patients facilitates findings which, under equal conditions, cannot be made with obese patients.

Inspection of the abdomen of a patient suspected of having an ectopic pregnancy is of some diagnostic value with thin patients but of little or no value with obese patients. The intra-abdominal mass,

which consists of the enlarged tube and, after perforation, of extravasated blood and coagula, causes a slight bulging in the hypogastric region on the affected side, detectable by careful comparison with the normal side. Cullen's sign, for which one should search at the time of inspection, is present in only a small number of cases.

Palpation of the abdomen reveals a soft abdominal wall, except when peritoneal irritation is caused by a hematoma within the peritoneal cavity and by the pressure of coagula on the peritoneum (even then the muscular rigidity is by no means as intensive as with acute inflammations). However, the most careful palpation is apt to cause pain, often severe, in the region of the pregnant tube.

Bimanual vaginal examination makes it possible to outline a soft mass, often without any definite demarcation, in either lower quadrant. This examination should be performed gently, because of the imminent danger of hastening rupture of the friable wall of the tube or causing more hemorrhage from an already perforated tube. These two dangers and the pain caused by this examination limit considerably the scope of the method. Great thickness of the abdominal wall makes bimanual vaginal examination almost useless for the diagnosis of ectopic pregnancy. In many cases details cannot be made out, and the only result is the finding of a "diffuse mass" ; but under favorable circumstances the findings are practically specific. The uterus is soft and enlarged but far below the size to be expected with a normal pregnancy of the same term. The findings in the region of the parametrium, tube and ovary before rupture differ from those after rupture. The period before rupture can be considered the dormant period.

Before rupture, the mass, represented by the enlarged tube, is usually not large enough to be palpated with ease. The pain experienced by the patient when the enlarged part of the tube slips underneath the examiner's fingers is often of more diagnostic value than the information obtained by the examiner through his own sense of touch. This pain is often elicited by pressure applied to the cervix, or to the posterior vaginal fornix alone. In some cases the enlarged tube can be made out clearly by palpation, and its nature can be identified when it is possible to demonstrate its mobility.

After the rupture, pain on palpation is occasionally diminished, unless a greater amount of extravasated blood accumulates, causing an irritation of the peritoneum. The pain at the time of perforation is intense and is often followed by collapse of the patient. The more or less circumscribed and fluctuating mass which is due to coagulation of the extravasated blood is distinctly palpable in a large majority of the cases; according to Behney [12] it is noted in 85.5 per cent of all cases.

12. Behney, C. A.: Extra-Uterine Pregnancy: A Study of One Hundred and Sixty-Seven Consecutive Cases, J. A. M. A. **95**:1557-1563 (Nov. 22) 1930.

DIAGNOSIS

As has been indicated, ectopic pregnancy produces clinical manifestations before rupture of the tube which are different from those after rupture.

(*a*) Before rupture of the pregnant tube the patient has a dull pain in one side of the hypogastric region. There are menstrual irregularities (either frequent, irregularly repeated uterine hemorrhages or complete absence of one or more menstrual periods). Abdominal distress, nausea or vomiting may occur, but never with such intensity as in the presence of acute inflammatory changes in the abdomen. Although the patient is able to go about and to perform her daily work, an enlarged uterus and a mass lateral to the uterus are palpable. The Aschheim-Zondek reaction is positive, but only in the presence of functioning chorionic tissue; after separation and death of placental tissue the reaction becomes again negative.

(*b*) After the rupture of the tube, most or all of the symptoms are intensified, and new ones aggravate the condition of the patient, who is in a state of shock associated with a crampy, severe pain in the lower part of the abdomen. Pain, dizziness and weakness force the patient to stay in bed. When the loss of blood reaches a certain amount, the patient appears anemic and the pulse is rapid and weak; the white blood count is elevated, but the red blood count is low. Severe pain is caused by palpation of the area of the pregnant tube. Irregularities of the menstrual history and a positive Aschheim-Zondek reaction make the diagnosis of ectopic pregnancy more definite, although, after perforation and death of placental tissue, the reaction will soon be negative. If the patient has any uterine hemorrhages at the time of examination, either before or after the perforation, the search for decidual shreds and chorionic villi is of great diagnostic help. The presence of decidual tissue is a definite proof of pregnancy, uterine or extrauterine, but its absence cannot be construed to the contrary. The presence of chorionic villi must undoubtedly be recognized as the most reliable sign of uterine pregnancy, and the diagnosis of ectopic pregnancy can be sustained only as long as no chorionic villi present themselves in the uterine discharge. In ectopic pregnancy the cervix becomes also soft and livid a short time after impregnation. Roentgen examination as an affirmative aid to diagnosis of ectopic pregnancy fails usually because the climax of the clinical progress is reached before the ossification centers of the embryo are demonstrable roentgenographically, which is possible not sooner than after the tenth or twelfth week of pregnancy.

It would be a mistake to explain the symptoms of secondary anemia only by the vaginal hemorrhage and not to take into consideration the possibility of intra-abdominal hemorrhage.

After perforation of the tube one can establish, according to the intensity of symptoms, two classes of condition: (*1*) the urgent, or acute, and (*2*) the nonurgent, or "chronic." 1. With the former, all the symptoms are well pronounced, and some of them reach an alarming climax: severe pain, prolonged collapse of the patient with slow recovery, anemic skin and mucous membranes, rapid and weak pulse, emptiness of the cutaneous veins, low blood pressure gradually falling in repeated readings, low red blood count and blood in the cul-de-sac, which is characterized by fluctuation in the posterior vaginal vault and is obtainable by paracentesis through the posterior vaginal fornix. Therefore, pulse, blood count and blood pressure must be taken frequently and must be charted in order to help in evaluation of the progress. 2. With the latter forms tubal rupture as a diagnostic problem is more puzzling than with the urgent conditions. In the nonurgent conditions the internal hemorrhage is not so profuse as to produce any alarming symptoms of secondary anemia; repair to the point of recovery often takes place without surgical intervention, and during the period of repair some of the patients are able to pursue their daily routine. Usually the only prominent symptoms are pain in the hypogastrium and vaginal hemorrhage, so that the condition is occasionally diagnosed as abortion or explained by some other erroneous diagnosis.

DIFFERENTIAL DIAGNOSIS

The pain caused by ectopic pregnancy may not stay close to the region of its origin but may radiate to other areas of the abdomen and sometimes even to the shoulder, thus making the differential diagnosis a difficult problem. A thorough history and a careful examination of the patient should disclose a pelvic origin for the pain. Although the type of pain is sometimes pathognomonic, it may occasionally mislead the diagnostician because of its radiation throughout the abdomen. The menstrual history must be discussed in detail with every woman who has abdominal symptoms. Ectopic pregnancy should always be considered and eliminated before the diagnosis of any other abdominal disease is definitely made in the case of a woman of the child-bearing age. The Aschheim-Zondek test should be performed whenever possible.

Normal Pregnancy.—Confusion of ectopic with normal pregnancy may occur when there is a uterus bicornis with the ovum implanted high up in one of the horns, in which case it is possible to palpate a spherical, well circumscribed and movable mass lateral to the midline. Absence of pain, hemorrhage and other manifestations makes the diagnosis of ectopic pregnancy dubious.

Abortion.—Abortion is characterized by profuse hemorrhage during elimination of the fetal parts and crampy pains in the midline of the

hypogastrium which the patient herself recognizes as pains in the womb. The pain associated with abortion is intermittent, corresponding with the periodic contractions of the uterus. After the critical moment of elimination of the fetus under labor-like pains the patient feels relieved except for occasional cramps and hemorrhages, which may be profuse if elimination of the uterine contents is incomplete. The great amount of blood and its bright color when the uterus expels its contents are indicative of an abortion; an undramatic spotting or a scanty hemorrhage producing brownish "old" blood indicates, most probably, an ectopic pregnancy, provided that the other findings support this diagnosis. By inspection of the masses of blood clot, especially after they are carefully rinsed in water, some of the lumps can be identified as decidua or villi. The presence of villi always indicates abortion, whereas decidual shreds are present with ectopic pregnancy as well as with abortion. In some cases of abortion, the fetus and the placenta can be identified easily. In ectopic pregnancy the uterus is smaller than a pregnant uterus before its emptying.

Rupture of an Ovarian Follicle.—This condition sometimes causes pains similar to those of ectopic pregnancy, but the other clinical symptoms are absent. Detailed inquiry regarding the menstrual history should be helpful, as repeated and regular occurrence of the same pain at intervals corresponding with the menstrual cycles is indicative of rupture of an ovarian follicle.

Ovarian Cyst.—An ovarian cyst can obviously attain the same size as a pregnant tube. It is firmer, but it is also movable and may sometimes cause menstrual irregularities. There is no attack of severe pain except when the pedicle is twisted; the growth is not as rapid as that of a pregnant tube. During the few weeks' observation when the diagnosis of tubal pregnancy is being considered, the mass will remain unchanged in size if it is an ovarian cyst and a crisis typical of perforation of a tube fails to appear. It is not advisable, however, to confirm the diagnosis of ectopic pregnancy by waiting for spontaneous perforation. Furthermore, an ovarian cyst is usually larger when it first causes discomfort than a pregnant tube is even at the time of its rupture. The long duration of subjective symptoms, the large size of the tumor and the menstrual history should give the correct interpretation of the clinical picture. The significance of the menopause in this connection is self evident.

An ovarian cyst with a twisted pedicle causes sudden pain and collapse of the patient, as does rupture of a pregnant tube. The mass of the cyst is better outlined on bimanual examination than is the diffuse mass caused by the hematoma after tubal rupture. The fluctuation, if palpable, indicates higher pressure in an ovarian cyst than in the mass

of the hematoma in ectopic pregnancy. An ovarian cyst will usually be palpable above the pelvic brim, which is a higher location than that attained by an ectopic pregnancy. Although leukocytosis may develop, there is no secondary anemia, and the pulse does not show the changes associated with ectopic pregnancy. The patient complains of distress in the lower part of the abdomen for a long time, sometimes for years, often stressing the occurrence of "indigestion" and uncomfortable sensations in the stomach.

Salpingitis.—This condition does not cause a sudden attack as does perforation of a pregnant tube, but it may have in common with ectopic pregnancy the leukocytosis and menstrual irregularities. The pain of ectopic pregnancy, radiating sometimes across the midline, may simulate a bilateral hypogastric pain which is significant of salpingitis. Fever, a septic appearance of the patient, peritoneal symptoms and enlargement of the tubes causing a bilateral pelvic mass are present in cases of acute salpingitis. There is no anemia in the beginning of salpingitis, but it may develop in the later stages. The uterus remains normal in size and consistency. A history of gonorrhea or a purulent vaginal discharge and the occasional finding of gonococci in the discharge are typical of salpingitis.

Uterine Fibroids.—When small, subserous and well demarcated from the uterus, or when intraligamentous, fibroids may sometimes give the same response to bimanual examination as an ectopic pregnancy. However, the fibroid is close to and movable with the uterus and is firmer than the pregnant tube. The history of the patient does not indicate pregnancy, and the physical signs of pregnancy are absent.

Intestinal Obstruction.—Obstruction or strangulation of an intestinal loop located in one of the lower quadrants may also begin in a stormy manner, similarly to perforating ectopic pregnancy, but there is no history or sign of an existing pregnancy. The history of a previous laparotomy is important, since intestinal obstruction is commonly secondary to adhesions resulting from an operation. If the symptoms produced by the obstruction (whether secondary to adhesions or to carcinoma) are of more than a few weeks' duration, ectopic pregnancy is improbable. If the symptoms are produced by a malignant obstruction, there may be signs of failing health, such as loss of weight and anemia; such signs will of course be absent with ectopic pregnancy. The intestinal symptoms, such as vomiting, constipation, retention of gas and stool and abdominal distention, are more prevalent with intestinal obstruction than with ectopic pregnancy and take a more alarming course. With ectopic pregnancy visible peristalsis is absent. The typical pains and symptoms of internal hemorrhage occupy the foreground of the clinical picture of a perforated ectopic pregnancy. Palpation of the sites favored by hernia, i. e., inguinal, umbilical and femoral, may some-

times clarify the diagnosis by the discovery of a small strangulated hernia, which, owing to its small size, may escape detection by casual inspection.

Gallstone Colic.—This condition in a heavy-set patient of the child-bearing age with a short costoinguinal distance and therefore a relatively low position of the gallbladder may arouse the suspicion of ectopic pregnancy but has nothing else in common with it except the severe pain.

Perforation of a Gastric Ulcer.—This occurs so rarely in women that its differentiation from ectopic pregnancy in the presence of symptoms of internal hemorrhage is seldom necessary.

Acute Appendicitis.—Acute appendicitis and perforated right tubal pregnancy have in common only the site of pain and the increased leukocyte count. Menstrual irregularities in a patient with a previously normal menstrual record are a strong indication of an ectopic pregnancy, and the finding of decidual particles is decisive proof of it. The onset of appendicitis is rarely characterized by sudden sharp pain and the collapse of the patient, both of which occur when the tube ruptures. Abdominal rigidity is more pronounced with appendicitis than with ectopic pregnancy. In appendicitis there is leukocytosis without anemia, but after rupture of the tube both leukocytosis and anemia are present. In cases of acute appendicitis the signs of pregnancy are absent, and no pelvic changes are found on bimanual examination. It must be borne in mind that in rare cases acute appendicitis may complicate an already existing pregnancy. The pain and tenderness of appendicitis are at McBurney's point, which is much higher than the area in which pain occurs with ectopic pregnancy. When the appendix is long and reaches down into the pelvis, the pains are localized correspondingly low and therefore can imitate those occurring in ectopic pregnancy. Vomiting, nausea and pain are predominant symptoms of appendicitis, though they do not occur in all cases. In cases of ectopic pregnancy associated with considerable hemorrhage the pulse is rapid and weak, whereas with appendicitis the pulse is rapid but of good volume.

Before rupture, pregnancy of the right tube must also be differentiated from so-called chronic appendicitis by evaluation of the menstrual history, the Aschheim-Zondek test, the location of the tenderness and other manifestations.

Calculus.—A urinary calculus impacted in the lower part of the ureter causes pain in the hypogastrium, but the pain projects into the region of the external genitalia, and because of stagnation of urine in the ureter and in the renal pelvis the pain is also experienced in the renal region of the affected side. Such a stone may also cause pain in the bladder or stabbing pain in the rectum. Cystoscopic and roentgen examination and the search for occult hematuria will give complete information about the condition of the urinary system. The urine for

analysis must be obtained by catheterization, because in the presence of uterine hemorrhage the uterine blood may mix with the urine, which originally was free of blood. In reading the roentgen picture it must be borne in mind that because of the associated infection symptoms may persist for several days after the stone has passed.

SUMMARY

Ectopic pregnancy can be diagnosed without any difficulty when all the symptoms are clearly developed: irregularities of a previously normal menstrual cycle, typical pains, general symptoms of pregnancy and typical physical and laboratory findings. The menstrual irregularities consist either of complete cessation of the menses or of irregular hemorrhages. Particles of decidua can be detected in the discharge; chorionic villi are evidence against the presence of ectopic pregnancy. The constitutional changes in a patient with an ectopic pregnancy are the same as those observed with a normal pregnancy. The pain is located in one of the hypogastric regions; it is dull and lasts for a few weeks (the dormant period), until a sudden sharp pain sets in (at the time of spontaneous rupture of the tube), followed by shock and vomiting. The uterus is only slightly enlarged, and a mass is palpable in the adnexal region lateral to the uterus. The Aschheim-Zondek reaction is positive. These symptoms are observed during the dormant period of the ectopic pregnancy, i. e., before perforation of the tube.

After perforation of the tube all these symptoms are overshadowed by shock, pain and symptoms of internal hemorrhage, with the typical changes in the pulse and blood picture. These symptoms can assume an alarming degree of intensity, endangering the life of the patient and thus constituting an emergency. On the other hand, there are instances in which the hemorrhage and shock are only moderate; in such cases the patient may recover without surgical intervention. In cases in which the hemorrhage is slight, it is obviously difficult to make a definite diagnosis of ectopic pregnancy. The patient does not appear dangerously ill but presents a clinical picture which makes it necessary to differentiate more carefully between ectopic pregnancy and other gynecologic and surgical diseases of the abdominal cavity.

The surgeon must always think of the possibility of ectopic pregnancy, unruptured or ruptured, when examining a patient of the childbearing age with symptoms of an acute or a subacute process in the lower part of the abdomen, because ectopic pregnancy in both of its stages shares many symptoms not only with gynecologic but with surgical diseases of the lower part of the abdomen. The diagnosis is difficult in many cases, as was explained in the introductory paragraphs of this article, and it often happens that the patient is first seen not by the gynecologist but by the surgeon.

CARCINOMA OF THE EXTRAHEPATIC BILE DUCTS

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Carcinoma of the extrahepatic bile ducts is a rare condition. Textbooks make few references to it, and the published reviews are fragmentary. Early diagnosis is essential, yet clinicians rarely consider it. The lesion may be found unexpectedly at laparotomy, and the surgeon is frequently at a loss as to the best methods of handling the situation. It is proposed to report 6 new cases of this condition and to correlate the data from these with those previously reported with a view to presenting a comprehensive picture of the morbid anatomic and clinical aspects of the disease.

Three earlier papers have been published dealing with cancer in closely related structures, namely, carcinoma of the suprapapillary portion of the duodenum (Stewart and Lieber) carcinoma of the infrapapillary portion of the duodenum (Lieber, Stewart and Lund) and carcinoma of the peripapillary portion of the duodenum (Lieber, Stewart and Lund).

ANATOMY

The extrahepatic bile ducts present such frequent variations in length, course, structure and relation that it is difficult to draw a sharp line between normal and pathologic anatomy. Also, topographic variations are dependent in part on functional states of the extrahepatic biliary system and of regional structures, such as the liver, gallbladder, pancreas, stomach and duodenum.

The right and left hepatic ducts appear in the transverse fissure of the liver and unite at an angle of 80 to 90 degrees, forming the common hepatic duct, which extends downward, backward and mesially in the gastrohepatic ligament. The common hepatic duct varies in length

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from 1 to 10 cm., averaging about 3.5 cm., depending on the level at which it is joined by the cystic duct. The duct crosses the portal vein and branches of the hepatic artery, and, as it emerges from the hilus, it overlies the anterolateral aspect of the portal vein, the hepatic artery proper usually coursing to the left of the duct.

The cystic duct, a continuation of the neck of the gallbladder, varies from 0.5 to 6.5 cm. in length, averaging 3 to 4 cm. The upper, easily movable, proximal portion has a redundant lining arranged in spiral folds to produce the valve of Heister. The lower, more fixed, distal portion of the duct is almost smooth and courses downward toward the left to join the hepatic duct. Pallin described high union, in which the confluence of the ducts lies 1 cm. or more above the upper border of the duodenum, and low union, at the level of the upper border of the duodenum or beneath it. In about half the subjects examined by Pallin, the cystic duct ran parallel with the hepatic duct for a variable distance and united with it about the upper border of the duodenum. Nuboer, following the classification of Ruge, Eisendrath and others, described three types of union: (1) the angular type seen in 36 per cent of cases, usually on the right of the hepatic duct; (2) the parallel type seen in 36 per cent of cases, usually deep behind the duodenum, and (3) the spiral type, seen posteriorly to the left in 28 per cent of cases.

The common bile duct varies from 4 to 10 cm. in length, averaging 6 to 7 cm., and is described in three parts. The suprapancreatic portion lies behind the duodenum and varies in length according to the point of confluence of the cystic and hepatic ducts. When this point of confluence is low the suprapancreatic portion is lacking. It descends along the right margin of the lesser omentum to the right of the hepatic artery, anterior to the portal vein. The pancreatic portion extends through a groove or tunnel in the posterior surface of the pancreas to its entrance into the descending duodenum. This segment is 3 to 5 cm. in length and is separated from the vena cava by connective tissue alone or by a thin layer of pancreas. The duodenal portion extends obliquely through the wall of the duodenum. A detailed description of this portion is found in the recent study by Dardinski.

CARCINOMA OF THE HEPATIC DUCT

Three new cases of carcinoma of the hepatic duct are reported. Fifty-six cases were abstracted from the literature, 32 of which were regarded as acceptable on the basis of a clinical history and gross and microscopic studies of the primary neoplasm.[1] Six additional cases,

1. Korczynski; Schüppel; Jenner (cases 1 and 2); Bezançon; Hesper, case 2; Claisse; Schuchardt; Schulze; Howald; Ingelrans; Porot; Rocco; Houssin;

(Footnote continued on next page)

probably authentic examples of this condition, were not utilized because of lack of a clinical history or because of insufficient data.[2] Eighteen cases were discarded because histologic studies were lacking in 15[3] and because of the possibility that the neoplasm may have been primary in the gallbladder in 2 and in the intrahepatic biliary ducts in another.[4] Thus there is a total of 35 cases of carcinoma of the hepatic bile ducts for analysis.

REPORT OF CASES

CASE 1.—J. K., a white man aged 82, was admitted to the Philadelphia General Hospital on Nov. 13, 1935, with pain, jaundice, bloody expectoration, abdominal distention, dark urine and putty-like stools of two months' duration. The jaundice appeared suddenly and increased progressively; it was preceded by attacks of severe, sharp abdominal pain. This radiated from the back over the entire upper part of the abdomen. There were increasing weakness, loss of weight, anorexia and vomiting. Physical examination showed impaired resonance, bronchial breathing and subcrepitant rales in both lungs. There was gaseous distention of the abdomen, with slight dulness in the flanks but no signs of fluid. The liver and spleen were not palpable. The urine was dark amber and acid, with a specific gravity of 1.012; it contained albumin but no sugar. The clinical impression was that of carcinoma of the common bile duct with peritonitis and bronchopneumonia. The patient lapsed into coma and died on November 15.

Autopsy was performed eighteen hours after death. The combined gross and microscopic diagnoses were: (1) scirrhous adenocarcinoma of the junction of the right and left hepatic ducts, with infiltration of the surrounding liver; (2) hydrohepatosis and marked jaundice; (3) arteriosclerosis of the aorta and coronary arteries, with acute myocardial degeneration; (4) bronchiectasis of the left lung; (5) biliary nephrosis, and (6) acute fibrinous peritonitis.

The peritoneal cavity contained 2,000 cc. of bile-stained serofibrinous fluid.

The stomach and duodenum showed no visible change. The small intestine contained black material and dark red blood.

The liver weighed 1,200 Gm. and was flabby and deeply bile stained. The surface was mottled with deep green markings, and varicose ducts were present, especially along the margins. Soft, nodular elevations on the surface corresponded to dilated ducts beneath. The liver cut with slightly increased resistance, revealing loose, friable parenchyma deeply mottled with green, brown and yellow. The cut surface showed many dilated ducts, which contained pale, thick mucous fluid.

Lapointé, Raymond and Merle; Adlercreutz; Gutowitz; Petrén, cases 14 and 16; Wahl, case 4; Wylegschanin; McLaughlin, case 4; Bosco; Shapiro and Lifvendahl, case 12; Milles and Koucky; David, cases 1 and 2; Lampert and McFetridge; Pérez Fontana, Anastasia and Castro, case 1; Hess and Faltitschek, case 2; Walters and Olson; Leiter.

2. Aufrecht, case 1; Netter; Jenner, case 3; Schmitt, case 3; Saltykow, case 7; Ikuta.

3. Bristowe; von Plazer, case 2; Bressy; Debove; Stieda, case 4; McGlinn, case 3895A; Petrén, cases 9 and 13; Blomström, case 2; Ramlau-Hansen, case 6; Harnisch, case 1; Cabot, case 20331; Hess and Faltitschek, cases 1 and 5; La Manna, case 2.

4. Willigk; Pittorino; Scudder and Richardson.

Both main intrahepatic ducts were obstructed at a point just proximal to their convergence. Here there were constriction, marked thickening and angulation, and the lumens were narrow and slitlike. It was doubted that bile could have

Fig. 1 (case 1).—Dissection of the hepatic ducts above and the common bile duct below. The dark probe is in the cystic duct, and the papilla of Vater is at the extreme bottom of the illustration. Note the constrictions in the hepatic ducts above and the thickened, fissured, irregular mucous membrane. × 1.

escaped spontaneously through these channels during life. The lining of the right, left and common hepatic ducts was thick, gray, fissured and granular (fig. 1). The gray tissue on the surface extended through the wall of the duct and was continuous with a firm gray tumor nodule, 3 cm. in diameter, embedded in the surrounding liver. Extensions of this tissue infiltrated along the large portal radicles for a short distance into the liver. The common bile duct below the lesion was neither thickened nor distended and emptied into an ampulla of Vater together with the duct of Wirsung, which also showed no visible change. The cystic duct

Fig. 2 (case 1).—Hepatic duct, showing an area of malignant transformation near the deep fissure to the left. The first change is a slight piling up of atypical epithelial cells on the surface. Then, in succession, there are the formation of several long, narrow and broad papillary projections and an invasion of atypical epithelial cells through the duct wall into the surrounding tissue. × 50.

opened into the common hepatic duct well below the point of obstruction. The gallbladder showed no visible abnormality; it contained 20 cc. of pale, opalescent mucous fluid entirely devoid of bile pigment. The cystic duct was unobstructed.

Several sections through the common and right and left hepatic ducts were studied microscopically. In most of these the mucous surface and underlying wall

of the duct were invaded by atypical epithelial cells. In other sections only a segment of the duct was involved by neoplasm, and an area of malignant transformation was clearly evident on the surface (fig. 2). The uninvolved duct was lined by thin, intact cells; the wall was slightly fibrotic and infiltrated with lymphocytes and monocytes, and the mural glands were slightly hyperplastic. The first significant change near the neoplastic margin was a piling up of cells on the surface, followed by formation of several long, papillary projections and extension of neoplastic cells through the wall of the duct into the surrounding tissue (figs. 2

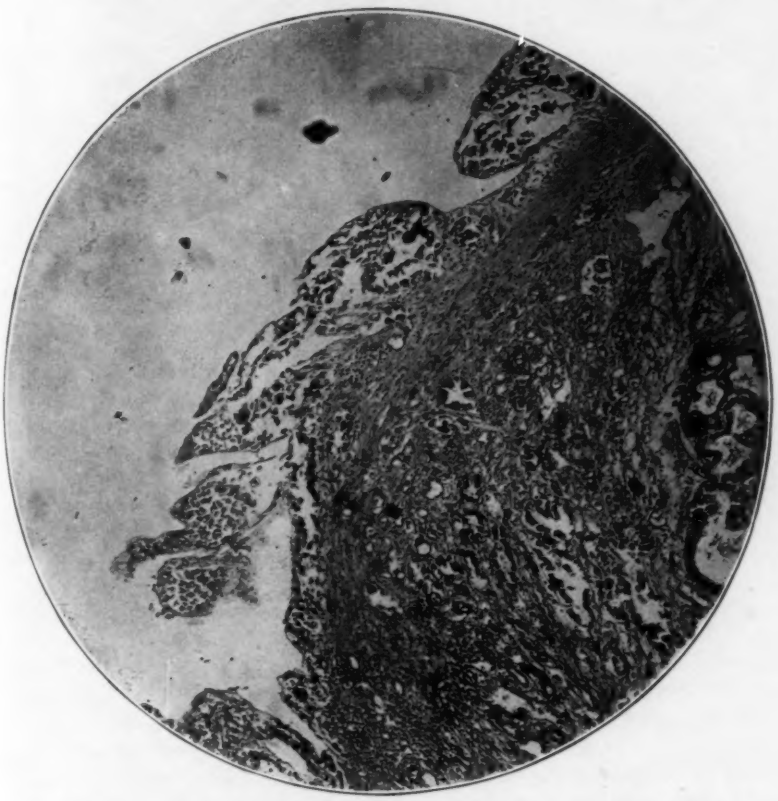

Fig. 3 (case 1).—Hepatic duct, showing broad papillary neoplastic excrescences on the surface with permeation of the wall and underlying tissue by atypical epithelial cells which are frequently arranged as acini. × 50.

and 3). The surface of the duct was slightly ulcerated in places, and the arrangement of the connective tissue of the wall was distorted.

The neoplastic cells varied considerably in size and shape, from single nucleated elongated cells to large giant cells containing four or more nuclei or a single large multilobed nucleus. Intermediate forms were cuboidal and columnar. The nuclei usually stained uniformly, only a few showing hyperchromasia. Occasional mitotic figures were seen. The cytoplasm was pink, granular, homogeneous or finely

vacuolated and sometimes contained droplets of mucin. Groups of five to twenty tumor cells were arranged in the form of small acini. A few large acini showed papillary formations and contained debris and mucus in their lumens. Other tumor cells occurred in the form of strands, clumps or imperfect acini with perineural and perivascular infiltration. The stroma was abundant and slightly vascular.

CASE 2.—E. C., a white man aged 52, was admitted to the Philadelphia General Hospital on Jan. 19, 1930. He had clay-colored stools, dark urine, jaundice, pruritis, gradually increasing weakness, loss of weight and dyspnea of four or five months' duration. Three days before admission to the hospital there was severe, intermittent abdominal pain accompanied by bloody stools. The abdomen was distended and tender. There was fulness in the flanks, and evidence of free abdominal fluid was noted. The liver was greatly enlarged. It had a sharp edge and a tender, nodular surface. The hemoglobin content of the blood was 60 per cent; the red blood cell count was 1,500,000, and the white blood cell count 20,000, per cubic millimeter, with 80 per cent polymorphonuclear cells. The value for blood sugar was 200 mg. and that for urea nitrogen 50 mg. per hundred cubic centimeters. The icterus index was 80, and the van den Bergh reaction was of the immediate direct type. At celiotomy, on January 23, biliary obstruction was assigned to a carcinomatous mass high in the hepatic duct, and cholecystostomy was performed. Mesenteric thrombosis, with about 12 inches (26.4 cm.) of hemorrhagic ileum, was also found. The patient died in shock the following day.

Autopsy was performed four hours after death. The combined gross and microscopic diagnoses were: (1) adenocarcinoma of the confluence of the right and left hepatic ducts, with metastases to the regional lymph nodes; (2) hydrohepatosis, with marked jaundice; (3) multiple hemorrhagic manifestations in the intestine and kidney; (4) surgical wound of the gallbladder; (5) acute degeneration of the myocardium; (6) biliary nephrosis; (7) hyperplasia of the spleen, and (8) hypertrophy of the prostate.

The liver weighed 2,260 Gm. and was yellowish green and tough. The gallbladder contained degenerated blood and disclosed a sutured incision at its fundus. The cystic duct was patulous. The common duct was small and when traced upward ended in an almost total obstruction at the junction of the three hepatic ducts. The obstruction was caused by a small, firm, indurated mass surrounding the ducts and projecting onto the mucous surface as small papillary excrescences. The ducts above the obstruction were enormously distended with clear, light yellow watery bile. The lymph nodes about the common duct were enlarged.

Microscopically, a section through the bile duct at the point of involvement showed the surface of the duct uneven and ulcerated. None of the normal epithelial lining cells remained. The surface was composed of connective tissue, inflammatory cells and tumor tissue which permeated the entire wall of the duct and infiltrated several large nerve fibers. The neoplastic cells were tall columnar, with moderately atypical epithelial elements. The cytoplasm was pink and granular. Most of the nuclei were fairly regular in size, shape and staining, although a few were markedly enlarged. Some cells were flattened and contained small nuclei. Mitotic figures were few. Most of the neoplastic cells were arranged in small acini. Others grew in clumps, strands and nests. The stroma was moderately abundant and infiltrated with mononuclears and lymphocytes. Blood vessels were few; there was little necrosis, and there was practically no hemorrhage.

There were small metastatic deposits in the lymph nodes.

The liver showed the features of biliary stasis, with degeneration and pigmentation in the inner lobule, biliary and focal midzonal necroses, slight bile duct and connective tissue proliferation and round cell infiltration. On the whole, the hepatic parenchyma was not altered markedly.

The kidney showed biliary pigmentation and slight degenerative changes in the tubular epithelium.

CASE 3.—P. D., a white man aged 63, was admitted to the Jefferson Hospital on April 16, 1923. There had been gradual loss of weight, strength and appetite for one and one-half years. Nausea with occasional vomiting occurred about once weekly, but pain was never a symptom. Loss of weight and strength was rapid in the five months before admission. Jaundice was first noted on the day before admission. On physical examination the liver was palpable as a nodular, irregular mass filling the epigastrium and the right side of the hypochondrium and extending 5 cm. below the costal cage. There was no tenderness or rigidity. The urine was acid, with a specific gravity of 1.005 to 1.012, and contained a trace of albumin, occasional casts, pus cells and bile; it contained no sugar or blood. The Wassermann reaction of the blood serum was negative. The hemoglobin content of the blood was 88 per cent; the red blood cell count was 3,900,000 and the white blood cell count 8,200 per cubic millimeter, and the color index was 1.12; about a month later these values were respectively 83 per cent, 3,500,000, 6,000 and 1.18. Analysis of the gastric contents showed a total acidity of 10 to 26, free hydrochloric acid of 9 and 12 at forty-five and sixty minutes respectively and absent in all other specimens; there were a trace of lactic acid and a trace of bile in all specimens, the latter indicating incomplete biliary obstruction. Roentgen examination of the gastrointestinal tract after a barium sulfate meal was performed on April 23 and showed a filling defect in the antrum of the stomach, producing irregularity of the sphincter. The stomach appeared irregular in outline, displaced to the left and fixed. At the end of six hours a medium amount of residue was present, and the duodenum appeared normal. The diagnosis was advanced carcinoma involving the lesser curvature of the antrum of the stomach. The temperature varied from 96 to 99 F., the pulse rate from 60 to 86 and the respiratory rate from 20 to 30. The patient left the hospital unimproved on June 4 and returned to work for three months. Then, because of increasing weakness, he entered the Philadelphia General Hospital on September 21. Death occurred one week later.

Autopsy was performed eighteen hours after death. The combined gross and microscopic diagnoses were: (1) primary adenocarcinoma of the common hepatic duct, with metastasis to the liver; (2) hydrohepatosis, with marked jaundice; (3) calculous cholecystitis; (4) infarcts of the spleen; (5) biliary nephrosis; (6) arteriosclerosis of the aorta and the coronary arteries; (7) terminal pneumonia; (8) myocardial degeneration; (9) peritoneal effusion, and (10) hyperplasia of the prostate gland.

The peritoneal cavity contained 6 liters of dark yellow serofibrinous fluid.

The liver weighed 2,830 Gm. It was firm, dark green and granular. The lobular markings were indistinct, and the lobules were surrounded by gray tissue. The lower third of the organ was occupied by a firm white growth 12 cm. in length, extending for 6 cm. from the lower margin into the liver tissue. The cut surface of the tumor was white, dry and fibrous. In the hepatic duct, near its origin, the primary tumor was found as a walnut-sized soft white nodule which projected into the lumen of the duct and merged with the larger mass within the liver.

The gallbladder was normal in size and contained tarry bile and several small friable calculi; similar calculi were present in the common bile duct.

The pancreas showed no visible change.

The prostate contained a number of small fibrous nodules.

The intestines showed congestion and edema of the mucous membrane.

Microscopically, the single section showing neoplasm was largely composed of connective tissue containing a large vein, a nerve and a necrotic area resembling liver tissue. Throughout the section were scattered nodules of atypical epithelial

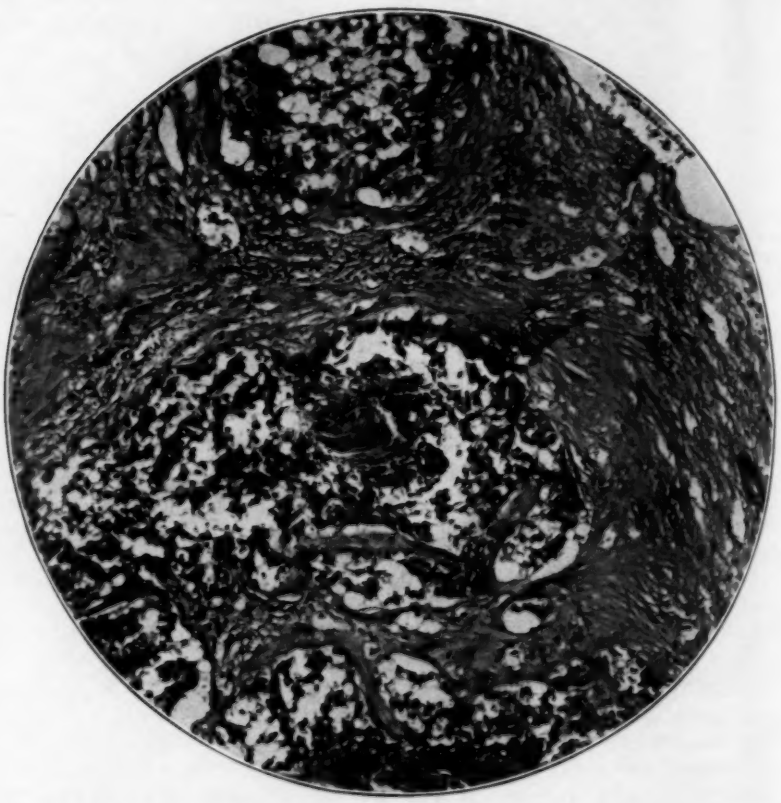

Fig. 4 (case 3).—Microscopic section of the tumor, showing scattered nodules of atypical epithelial cells embedded in dense hyalinized connective tissue. × 100.

cells. These nodules were fairly uniform in size and structure. The atypical epithelial cells were columnar or cuboidal, with deeply stained granular cytoplasm and large, fairly regular hyperchromatic nuclei; mitoses were rare. The nodular areas were composed of atypical epithelial cells arranged as acini or growing solidly. In the larger nodules one half to two thirds of the inner portion was necrotic and contained blue-staining deposits (fig. 4). The stroma adjacent to the tumor cells was dense and collagenous, but elsewhere it was loose, vascular and infiltrated with inflammatory cells in focal areas.

The liver showed marked pigmentation and slight degeneration in the inner part of the lobule, with moderate fibrosis, bile duct proliferation and slight irregularity of the surface.

AGE AND SEX INCIDENCE

Of the 35 patients, 29 were men ranging in age from 29 to 82 years, with an average of 56.5 years, and 6 were women ranging in age from 31 to 59 years, with an average of 45.2 years. In the younger age group were 2 men, aged 29 and 32 respectively, and 1 woman, aged 31.

Three cases of primary carcinoma of the hepatic duct were found in a series of 22,152 autopsies performed at the Philadelphia General Hospital between Jan. 1, 1920 and Dec. 31, 1936, an incidence of 0.0135 per cent of all autopsies. Carcinoma was found in 2,687 cases in this series, an incidence of 0.11 per cent of all carcinomas.

MORBID ANATOMY

The neoplasms in this series of cancer of the hepatic ducts can be divided into three groups on the basis of the morbid anatomic characteristics, namely, local (26 cases), diffuse (in 8 cases) and combined local and diffuse (in 1 case).

A local tumor was present in the following sites: at the bifurcation of the common hepatic duct (13 cases); at the bifurcation of the common hepatic duct and the lower portions of the two rami (6 cases); at the lower end of the common hepatic duct (4 cases), and at the left hepatic ramus (2 cases). In 1 case the location was not stated. The bile ducts were completely obstructed by neoplasm in 13 cases and incompletely obstructed in 5; in the remainder this point was not investigated. In 4 cases the local tumor consisted of a soft, friable polypoid nodule, firmly attached to the wall of the duct by a pedicle or a broad base and elevated above the mucous surface so as to fill the lumen. The majority of the local tumors, however, were small, annular, constricting gray or yellowish white growths averaging 2 cm. in diameter, with thickening of the wall of the duct up to 2 cm. The mucous surface was either smooth or finely granular, excrescences or fissures and ulceration were observed in 4 cases. Externally, a well defined tumor mass was usually observed, which in 1 case extended into the liver as a wedge-shaped nodule. In several cases the lesion on palpation was mistaken for a gallstone. In others it was suggestive of benign fibrous stricture; one operator dilated it in the mistaken belief that he was dealing with a chronic inflammatory process. The two tumors originating in the left hepatic duct were apparently of this type. In Rocco's case, a small, hard, stenosing carcinoma of the left hepatic duct permitted the passage of a fine sound. In McLaughlin's case 4, a firm yellowish white tumor completely surrounded and invaded the left hepatic duct, almost occluding its lumen.

A probe forced through this mass met with an obstruction 2 cm. above the bifurcation of the common hepatic duct, and withdrawal was followed by the discharge of thick, purulent matter from above; the right hepatic duct was distended, and its orifice at the junction with the left branch was almost completely occluded by tumor.

The diffuse type of growth was found in the region of the bifurcation of the common hepatic duct in 1 case, in the region of this bifurcation and extending upward along the two rami in 6 and involving the entire length of the common hepatic duct in 1. The neoplastic involvement in these cases was diffuse and widespread, and the peripheral limits were ill defined. The neoplastic tissue was firm, white and annular, producing marked stenosis and rigidity of the ducts, while the mucosa was granular, fissured and sometimes ulcerated. In several instances the growth extended along the large bile ducts into the liver, forming either a continuous large solitary mass or multiple pea-sized nodules.

A combined local and diffuse type of growth occurred in Korczynski's case. The wall of the beginning portion of the common hepatic duct was 2 mm. thick, and on its inner surface were diffuse deposits of a rather soft, succulent reddish yellow tissue. About 2 cm. below these was a 4 mm. tumor on the mucous surface.

In no case in this group was there neoplastic involvement of the cystic duct or of the common bile duct. The cystic duct was partially compressed by extrinsic masses in 1 instance, and in another the base of the cystic duct was completely obliterated by chronic inflammatory scar tissue. Biliary calculi were present in eight locations in a total of 5 cases, in the gallbladder in 4, in the common bile duct in 2 and in the cystic and intrahepatic bile ducts in 1 each. The fluid in the distended ducts proximal to the point of obstruction was described as clear and white in 3 cases and purulent in 1.

The liver showed some degree of biliary stasis in all cases, hepatic enlargement in the majority and biliary cirrhosis in 9. Hepatic abscesses were reported in 1 case, purulent cholangitis in 2 and subphrenic abscess in 1. Multiple white infarcts were present in the liver in 1 case. The finding of hepatic infarction is extremely unusual, for of a large number of cases of obstructive jaundice in human beings examined by two of us (Lieber and Stewart) and from a review of the literature on hepatic infarction (Lund, Lieber and Stewart) this was the only clinical example of an infarct of the liver encountered in the presence of biliary stasis. In animals, on the contrary, infarcts of the liver are not uncommon after experimental ligation of the common bile duct (Stewart and Lieber).

Usually the gallbladder contained watery gray, white or opalescent fluid and was not distended. In 1 case the content was thin icteric fluid,

and in another, thick tarry bile. This indicated either incomplete obstruction at the level of the tumor or that accessory ducts passed directly from the liver into the gallbladder. No case was found in which such accessory ducts obviated the full effects of biliary stasis. The gallbladder was empty and collapsed in 2 cases and distended in 7 cases, in all of which the cystic duct emptied below the primary tumor. The mechanism responsible for cholecystic distention was unexplained, although blockage of the cystic duct may have been effected by traction of the primary tumor or by compression due to extrinsic pressure (e. g., by enlarged lymph nodes). In 1 case it was obliterated by scar tissue. The contents of the gallbladder were blood stained in 3 cases, in 1 of which an incision had been made previously. Evidences of cholecystitis with atrophy were present in 9 cases, in 4 of which biliary calculi were also found. Pericholecystic adhesions were present in several instances.

Free fluid in amounts of 1 to 6 liters was present in the peritoneal cavity in 11 cases; in the majority it was bile stained. The effusion in 1 case contained blood. In 2 cases there was evidence of recent fibrinous peritonitis.

Neoplastic spread occurred in 17 cases, as follows: to the liver (12 cases); to the regional lymph nodes (7 cases), and to the pancreas, the gastrohepatic ligament and the mediastinum (1 case each). In 10 cases of hepatic invasion the tumor extended directly along the lesser ducts into the liver. In 1 instance the hepatic extension consisted of a single large, firm mass 12 by 6 mm. directly continuous with the primary growth. Discrete metastases were noted in the liver in the cases reported by Rocco and by Walters and Olson.

HISTOLOGIC PICTURE

All the neoplasms were glandular carcinomas. In the majority, the atypical epithelial cells were cylindric or cuboidal. Some degree of pleomorphism was present in 5 cases, in 1 of which the tumor was described as a solid alveolar carcinoma. Giant cells were present in 1 case. Nuclear hypertrophy and hyperchromasia were usual. Mitotic figures were noted in only 4 cases. Acinar structures were present in 27 cases, with marked variation in size and shape in several and the formation of microcysts in 2. Papillary projections into the acini occurred in 4 cases. Mucinous material was present in varying amount within and between the cells and within the acini in 4 cases, in 2 of which the tumors were designated as mucinous adenocarcinoma. Perineural invasion occurred in 2 cases. The stroma was abundant in the majority, the scirrhous character being an outstanding feature. Areas of hemorrhage, necrosis or inflammatory reaction were rarely described.

CARCINOMA OF THE CYSTIC DUCT

Twenty-seven cases reported as examples of primary carcinoma of the cystic duct were abstracted from the literature. These were studied critically to eliminate the gallbladder and other sites as possible primary sources of the neoplasm. These reported primary neoplasms of the cystic duct were grouped as follows:

Group I.—In 14 cases of tumors in the cystic duct there appeared also to be gross neoplastic involvement of the gallbladder, confirmed microscopically in 5 instances (Vautrin; Chini; Licini; Pellegrini; Dalla Valle, case 2; Satta, cases 1 and 2; Schmidt; Ortiz and Coffigny; Dialti; Cailliau; Ramlau-Hansen, case 2; Shapiro and Lifvendahl, case 15, and Hess and Faltitschek, case 3).

Group II.—In 7 cases, histologic studies of the neoplasm in the cystic duct or in the gallbladder were lacking. The latter organ was described only once; the wall of the gallbladder was thickened, but the mucous membrane appeared normal (Rösch; Etienne; McGlinn, cases 3213A and 839B; Dalla Valle, case 3; Bertini; Bailey).

Group III.—In 5 cases, although gross and microscopic studies were made of the neoplasm in the cystic duct, microscopic studies of the gallbladder were lacking. The gallbladder was described grossly in only 1 case, in which it was small and thick (Petrén, case 46; Wohlwill; Saltykow, case 8; Hellner; McLaughlin, case 1).

Group IV.—In 1 case a small localized polypoid tumor of the cystic duct was found, together with metastases in the liver, in the abdominal lymph nodes, in Virchow's node and in the rectal wall. The neoplasm was designated histologically as carcinoma solidum. The gallbladder was not described grossly or microscopically and it appears that the rectum was insufficiently considered as a possible primary source for the growth (Shapiro and Lifvendahl, case 14).

We are, therefore, unable to consider any of these cases as indisputable instances of primary carcinoma of the cystic duct. Obviously, extreme care must be taken to exclude cancer of the gallbladder, pancreas, stomach, duodenum and rectum in order to substantiate the case. Occasionally primary carcinoma of the gallbladder infiltrates the cystic, hepatic and common bile ducts and even extends down through the ampulla of Vater into the duodenum. Neoplasms at the confluence of the bile ducts (to be dealt with in the next section) possibly may have taken origin from the cystic duct, secondarily extending to the hepatic and common bile ducts. However, no proved case has yet been reported of a malignant growth arising primarily in the cystic duct and remaining sufficiently localized within the confines of that structure to make the origin of the tumor unquestionable.

CARCINOMA AT THE CONFLUENCE OF THE EXTRAHEPATIC BILE DUCTS

Two new cases of carcinoma at the confluence of the common hepatic duct, the cystic duct and the common bile duct are reported. One hundred and forty cases were abstracted from the literature, 46 of which were regarded as acceptable,[5] the report of each including a clinical history and gross and microscopic studies of the primary lesion. Twelve additional cases, although probably authentic examples of this condition, were not included in the present study owing to the lack of a clinical history or to insufficient details.[6] Forty-seven cases were not utilized because histologic studies were lacking.[7]

Of 35 cases, the possibility remained that the neoplasm was primary in the gallbladder in 32 cases[8] and in the stomach in 3.[9] The reports of the 2 new cases follow, and the data obtained from these, together with those from the 46 acceptable cases of this condition, are subjected to analysis and summary based on a total of 48 cases in this group.

CASE 4.—M. M., a white man aged 64, was admitted to the Philadelphia General Hospital on July 11, 1927, with deep jaundice and extreme emaciation. A detailed history was not obtained because of difficulties with language. The present illness had begun eight months previously. Pain had not caused complaint.

5. Laugier; Chouppe; Silver; Schreiber; Bradbury; Yamagiva, case 1; Brenner, case 1; Bruno; Lecène and Pagniez, cases 1 and 2; Devic and Gallavardin, case 2; Koerber; Uliszewski, case 2; Miodowski, case 6; Huguenin; Kehr; Donati; Scagliosi, case 1; Pepere; Weber and Michels; Löschke; Cade and Pallasse; Borelius, case 1; Wising and Key; Morian, case 1; Spindler; Lameris; Pallin, case 4; Prat, case 2; Dalla Valle, case 1; Wahl, case 5; Senokuchi; Kurths; Vallery; vander Veer; Pliverić; Carnot; Mondor; Shapiro and Lifvendahl, case 13; McLaughlin, cases 2 and 3; Lee and Totten, case 1; Cabot, case 21, 122; Romano and Rey; Quénu and Gasne; Cabot, case 22492.

6. Moore, case 2; Brenner; Jordan; Cotte; Saltykow, case 5; Nyström; Duplant; Thévenod and Finck; Shapiro and Lifvendahl, case 7; Konjetzny; Fehr; La Manna, case 4.

7. Durand-Fardel; Bourceret and Cossy; Aufrecht, case 2; Bernheim and Simon, case 2; Niemeyer; Bohnstedt; de la Camp, cases 2 and 3; Géraudel; Tesson; Patel and Jaboulay; Tuffier; Gallavardin; Junquet, cases 9 and 10; Warfvinge and Wallis; Åkerbloom; Berg; Stieda, case 5; Littlewood; Pallasse and Perret; Desjardins; Flügger; Dressen; Petrén, case 18; Koechlin, case 2; Amberger; Dalla Valle, cases 5, 6, 7, 8, 9, 10, 11 and 12; Copello; Brocq and Maduro, cases 2 and 3; Cabot, case 13521; Blomström, case 1; Cabot, case 16071; Ferrario; Ramlau-Hansen, cases 3 and 4; Payan, Monges and de Vernejoul; Romano and Rey, case 2; La Manna, case 3.

8. Frarier; Rémy; Haas, cases 1 and 2; Fazio; Anderson and Dewar; Jourdan; Brunswig; Kleinertz; Häni, cases 5 and 6; Miodowski, cases 2 and 3; Planteau and Cochez; Martin, case 2; Sherrill, cases 1 and 2; Lecène; Cailliau; Zuccóla, case 5; Saltykow, case 6; Dalla Valle, cases 2, 3 and 4; Brocq and Maduro, case 1; Dimitriu; Gutiérrez; Ramlau-Hansen, case 1; Chabrol and Waitz; Pérez Fontana, Anastasia and Castro; Lamattina; Bailey, case 18.

9. Haas, case 3; Griffon and Leven; Gleiss.

The abdomen was prominent and bulging; a mass was present in the right side of the hypochondrium, and there was evidence of free peritoneal fluid. The chest was emphysematous. Resonance at the base of the left lung posteriorly was impaired. Edema of the lower extremities was marked. The urine was alkaline; its specific gravity was 1.012, and it contained a faint trace of albumin and occasional hyaline casts. The van den Bergh reaction was positive, and the icteric index was 150. Paracentesis yielded 4,000 cc. of icteric fluid. The temperature varied from 97 to 98.3 F., the pulse rate from 70 to 88 and the respiratory rate from 20 to 28. The clinical diagnosis was carcinoma of the head of the pancreas. The patient died on July 18.

Autopsy was performed four hours after death. The combined gross anatomic and microscopic diagnoses were (1) carcinoma of the extrahepatic bile ducts, with metastases to the lymph nodes, the liver and the peritoneum; (2) hemorrhagic peritoneal effusion; (3) hydrophepatosis, with marked jaundice; (4) intestinal hemorrhage; (5) bile pigmentation of the kidney; (6) cystic goiter; (7) dilatation and degeneration of the heart, and (8) terminal pneumonia.

The peritoneal cavity contained 3,500 cc. of bloody fluid. Many small gray nodules studded the peritoneum of the small and large intestine, diaphragm and pelvis. The pericardial cavity contained 50 cc. of bile-stained fluid.

The liver weighed 1,530 Gm. The surface was finely granular, the edges were sharp and the parenchyma was dark green, firm and tough. A number of firm gray circumscribed nodules were superficially located beneath the capsule. The branches of the portal vein and bile ducts were tremendously dilated. The gallbladder contained a small amount of brown viscid fluid. A very narrow lumen could be traced through the common bile and hepatic ducts, and the cystic duct was totally obstructed. Near the ampulla of Vater the lumen of the common bile duct again widened. Along the course of the obstruction the walls of the affected ducts were replaced by tough, gray homogeneous tissue of cartilaginous consistency.

The lymph nodes along the greater curvature of the stomach were enlarged and on section were gray and homogeneous.

A microscopic section was obtained of the bile duct and an adherent piece of colon. The inner surface of the duct was uneven and ulcerated in places. The surface cells showed autolysis, but immediately beneath were atypical epithelial elements and inflammatory cells. The wall of the duct was markedly thickened by dense fibrous tissue, which was infiltrated by atypical epithelial cells. The line of adhesion between the bile duct and the colon was infiltrated by tumor tissue, as was the outer coat of the colon, but the intestinal mucous membrane was intact. The tumor cells consisted of atypical columnar epithelium arranged in the form of acini. Many were flattened and irregular in size, shape and staining. The nuclei were large, oval and frequently pale and the cytoplasm was pink and granular. A few mitotic figures were observed. Irregularity of the tumor cells appeared greatest where they permeated the dense connective tissue wall of the bile duct. Some cells contained single large vacuoles. Most acini were small and varied in shape, with degenerated material in the center. The connective tissue stroma was abundant, vascular and infiltrated with focal collections of lymphocytes.

The kidneys showed marked bile pigmentation and slight degenerative changes in the tubular epithelium.

The liver showed the features of far advanced biliary obstruction, with pigmentation and degeneration in the inner portion of the lobule, focal midzonal and biliary necrosis, proliferation of small bile ducts and marked cirrhosis, with irregularity of the lobular architecture.

CASE 5.—J. R., a white man aged 75, was admitted to the Philadelphia General Hospital on Sept. 3, 1921, complaining of painless progressive jaundice, increasing weakness and loss of appetite for five months. The jaundice varied somewhat in intensity but never completely disappeared. Recently there had been marked pruritus. The stools were clay colored during all this period, but there was no constipation or diarrhea. A mass the size of a hen's egg lay in the right upper abdominal quadrant, but neither the liver nor the spleen was palpable. There was no fever at any time. The urine was alkaline, had a specific gravity of 1.010 and

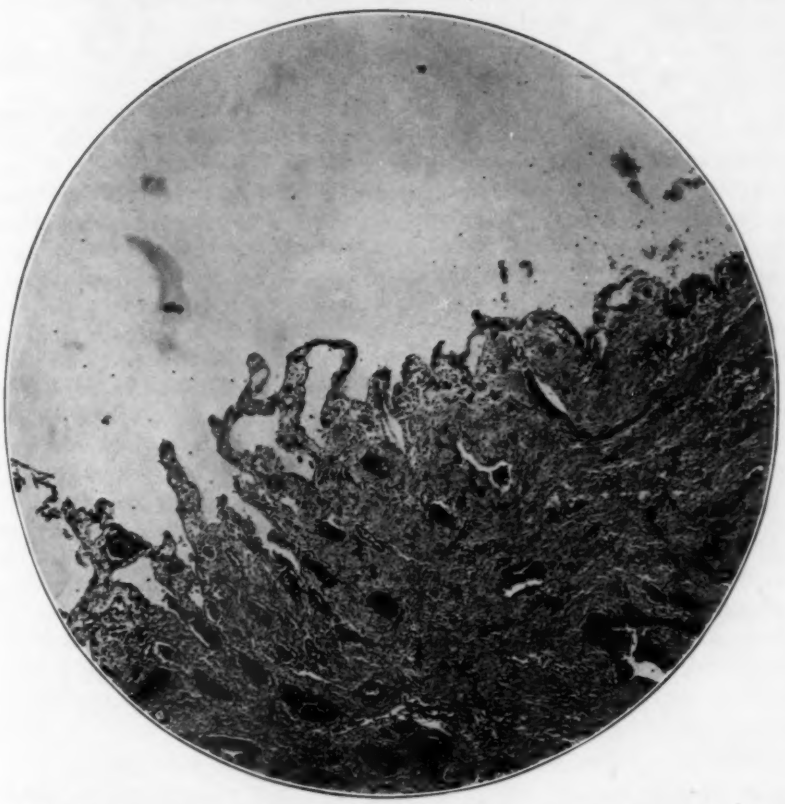

Fig. 5 (case 5).—Bile duct, showing numerical increase and hypertrophy of surface villi and collections of atypical epithelial cells below the surface. In a few places narrow fissures extend into the depths of the wall. × 50.

contained bile. A clinical diagnosis of carcinoma of the head of the pancreas was made. The jaundice deepened, and increasing evidence of ascites was noted; weakness was progressive, and the patient died on September 23.

Autopsy was performed four hours after death. The combined gross and microscopic diagnoses were: (1) adenocarcinoma, primary at the confluence of the common, cystic and hepatic ducts, with extension to the pancreas; (2) hydrohepatosis, with marked jaundice; (3) biliary cirrhosis of the liver; (4) biliary nephrosis; (5) generalized passive venous congestions; (6) anasarca, and (7) arteriosclerosis of the aorta and the coronary arteries.

The peritoneal cavity contained 1,000 cc. of slightly turbid fluid, and the serosa was smooth and glistening. It was not possible to express bile into the duodenum by pressure on the gallbladder. A probe passed up the common bile duct encountered an obstruction 4.5 cm. from the ampulla of Vater. The gallbladder was enormously distended with clear, colorless fluid. It measured 19 cm. in length. The cystic duct was also distended, and its outlet into the common bile duct was completely blocked. The hepatic duct was distended with clear yellow bile. It was totally obstructed by a firm tumor 5 cm. in length and 2 cm. wide; this arose 4.5 cm. from the ampulla and obstructed all three ducts at the confluence. Here the mucosa was thickened by tumor tissue which extended for a short distance into the pancreas. The liver weighed 2,130 Gm. The cut surface was green, the lobular markings prominent and the bile ducts markedly dilated.

A section of the bile duct, obtained through an area showing malignant transformation, was studied microscopically. Most of the epithelium along the normal portion of the duct was autolyzed. There was an increase in number and hypertrophy of the surface villi, and in the stroma of these were collections of atypical epithelial cells. In a few places narrow fissures extended into the depth of the wall of the duct, but no ulceration was observed here (fig. 5). Many atypical epithelial cells were tall and columnar, having abundant acidophilic granular cytoplasm and basally situated hyperchromatic nuclei. Other cells varied considerably in size, shape and staining and tended to become flattened, especially where the acini were distended. Other cells grew in nests and strands which permeated between the connective tissue fibers through the entire thickness of the duct and into the lymphatic vessels. Mitotic figures were infrequent. The stroma was abundant and dense, containing few vessels. Necrosis and hemorrhage were slight, and there were no marked inflammatory changes.

The liver showed advanced biliary cirrhosis. The lobular architecture was distorted; the central veins were displaced, and the cords of the cells were irregularly arranged. There was marked proliferation of small biliary ducts and of connective tissue which invaded the lobules. The medium-sized bile ducts were distended, and their walls were thickened and fibrotic. The parenchymal and phagocytic cells of the liver were deeply pigmented. The hepatic cells were degenerated and atrophic, and many areas of biliary necrosis were seen.

AGE AND SEX INCIDENCE

The patients in the reported cases included 32 men ranging in age from 45 to 81 years, with an average age of 61.5 years, and 16 women ranging in age from 38 to 72 years, with an average age of 64.7 years.

The 2 cases of carcinoma of the confluence of the ducts occurred at the Philadelphia General Hospital in a series of 22,152 autopsies (0.009 per cent), of which 2,687 showed carcinoma (0.074 per cent of all carcinomas).

MORBID ANATOMY

The common hepatic, cystic and common bile ducts were involved jointly by neoplasm in 38 cases. Of the remaining 10 cases there was no mention of involvement of the cystic duct in 6 or of the hepatic

duct in 2, whereas in 2 cases the cystic duct was said to be entirely free of neoplasm. In Schreiber's case, although a cherry-sized tumor projected into the lumen of the common bile duct at the point of union with the hepatic and cystic ducts, the cystic duct was patent and opened just below the involved hepatic duct. In Miodowski's case 6, the common hepatic duct was the seat of an annular tumor the size of a goose egg, which extended downward to involve the common bile duct; between these two areas of involvement, however, a 3 mm. segment of the bile duct was curiously free from neoplasm and corresponded exactly to the point of entrance of the cystic duct.

The neoplasm formed a local tumor in 27 cases and a diffuse growth in 21.

The local tumors were of two types. One consisted of a single elevated nodular projection above the mucous lining. The other type caused annular constriction and thickening of the wall of the duct; occasionally flat excrescences formed on the mucous surface, but no elevated projection was described. Most of the local tumors were said to be the size of a hazelnut; a few were pea sized, and two were the size of a hen's egg. The only stated measurement was 5 by 2 by 2 cm. The tumors were gray or white and hard, fibrous or cartilaginous in consistency. The surface was slightly roughened, granular or papillary, and was raw and necrotic in a few instances. In 2 cases the mucous membrane was smooth, and the tumor was thought to arise from glands in the wall of the duct. In 1 case a localized, elevated nodule exhibited a ball-valve action which arrested a sound passed from below but not one passed from above. An incorrect diagnosis of biliary calculus was made at laparotomy in 2 cases. The rate of growth of the neoplasm was recorded in 2 instances by direct inspection through a laparotomy incision. One tumor did not enlarge perceptibly during six months; the other grew from the size of a walnut to that of a hen's egg in nine months.

The diffuse type of neoplastic involvement was characterized by excessive thickening of the wall of the duct by gray, white or yellowish white firm, fibrous or cartilaginous tissue. Peripherally this type of growth was poorly defined. In 1 case, tumor tissue extended into the transverse fissure of the liver. The lining of the duct in the involved portion was either smooth or studded with diffuse excrescences, friable vegetations, soft polypoid masses (varying in size from that of a cherry to that of a goose egg) and small ulcers. Sometimes the lesion was mistaken grossly for a benign fibrous stricture of inflammatory origin.

The bile ducts were completely obstructed in 8 cases, incompletely obstructed in 18 and probably incompletely obstructed in the remainder. Since it is difficult precisely to determine the patency of bile ducts at

postmortem examination, the accuracy of these figures is questionable. Clinical data may indicate complete obstruction, and yet evidence of patency may appear at autopsy. The upper limit of obstruction occurred in the lower segment of the common hepatic duct in 37 cases, in the mid-duct in 2 and at the upper end of the duct in 4. In the remaining 5 cases the point of obstruction extended to the left hepatic ramus in all and to the right hepatic ramus in 2. Above the obstruction the bile ducts were thin and maximally dilated. The dilatation extended upward, involving the lesser intrahepatic radicles, and occasionally formed varicosities on the surface of the liver. The contents of the intrahepatic ducts were light green or yellow in 6 cases, clear and colorless in 3 and purulent in 2. The liver usually was enlarged and showed the gross characteristics of biliary stasis. Marked cirrhosis was present in 10 cases, in 2 of which the liver was small. Hepatic abscesses were present in 3 instances.

The lower limit of obstruction was variable. Below this limit the common bile duct regained its usual caliber; its mucous membrane was smooth, usually not bile stained and sometimes covered with clear mucus.

The orifice of the cystic duct was completely obstructed in 35 cases, partially obstructed in 5 and uninvolved in 2. In 6 this point was not commented on. In 1 case the entire length of the cystic duct was totally obliterated by scar tissue, so that not even its lumen could be identified with certainty. In 3 others this duct was obstructed by a combination of calculus and neoplasm. Proximal to the point of closure the cystic duct and gallbladder were distended in 25 cases. The gallbladder averaged about twice normal in volume, being 19 cm. long in 1 case and the size of a man's fist in another. It contained from 50 to 500 cc. of fluid, which was white or colorless in 12 cases, light colored in 8 and thick and tarry in 2. With tarry bile in the gallbladder, the possibility of a ball-valve action of the neoplasm was considered as permitting bile to enter the viscus and become concentrated there but not to leave it. The other alternative postulates an anomalous duct from the liver discharging bile directly into the gallbladder and thus circumscribing the obstruction of the cystic duct. The contents of the gallbladder were purulent in 3 cases and thick yellow and inspissated in 2. In 13 cases, the viscus was either undistended or small and atrophied, and the cystic duct was completely obstructed in all but 3 of these. Biliary calculi were present in the gallbladder in 9 cases, in the cystic duct in 2 of these and in the cystic duct only in another case. Evidences of cholecystitis were recorded in 10 cases, with empyema of the gallbladder in 4 and associated calculi in 4 others. In 1 case, a rent 2 by 1 cm. was present on the posterior surface of the gallbladder; the viscus was empty, and 2 liters of partially clotted blood was free in the abdominal cavity.

Peritoneal effusions occurred in 13 cases in amounts of 1 to 4 liters of fluid, with bile in 3, blood in 2 and inflammatory elements in 3, in 1 of which the material was frankly purulent. In Senokuchi's case, the abdominal cavity was filled with 2,000 cc. of colloid-like material, and the serosa was everywhere covered with colloid masses mixed with fibrinous and fibrous strands resulting in extensive visceral adhesions. In the upper part of the abdomen, adhesions were present in 10 cases, to the liver, the gallbladder, the colon, the anterior abdominal wall and the great omentum. Fibrinous adhesions were present in 4 cases, in 2 following laparotomy.

Extensions or metastases of the primary tumor were found in 22 of the 48 cases and were distributed as follows: in the liver (16 cases); in the regional lymph nodes (10 cases); in the gallbladder (2 cases); in the lung (2 cases); in the peritoneum (2 cases), and in the pancreas, the kidney, the wall of the portal vein, the gastrohepatic ligament, the spleen and the bronchial lymph nodes (1 case each). The hepatic metastases were in general similar to those from other neoplasms of the alimentary tract. In a few cases direct infiltration of hepatic substance resulted from growth along the rami of the hepatic duct. In Senokuchi's case of mucinous carcinoma there were extensive peritoneal involvement and metastases to the spleen. The 2 cases in which there were metastases to the gallbladder are of interest. In McLaughlin's case 2, the gallbladder was small and thick walled, and in one area, near the fundus, the mucous membrane was yellowish white and elevated above the general surface level; it was adherent to an underlying dense tumor nodule continuous with the adjacent liver tissue. Microscopic examination showed extension of carcinoma from the liver into the gallbladder, with involvement of all coats except the mucosa. Similarly, in Cade and Pallasse's case, the gallbladder was dilated and tense, and at its external superior pole a neoplastic nodule united it with the liver.

HISTOLOGIC PICTURE

All the neoplasms at the confluence of the bile ducts were glandular carcinomas. The cells were essentially cylindric, columnar or cuboidal, although in many cases they were flattened, and in 1 instance goblet cells were noted. Pleomorphism was marked in 8 cases, and one neoplasm was entirely undifferentiated. The cells reproduced acinar structures in 37 cases, with papillary infoldings in 3; they grew in the form of clumps, strands, cords or nests in 20 other cases. Mitotic figures were observed in only 6 cases. Considerable quantities of mucinous material occurred in and between the cells and in the acini in 3 cases, in all of which the tumors were designated as mucinous adenocarcinomas. Marked dilatation of acini with the formation of microcysts

was observed in a single case. The stroma of these tumors was usually abundant, although a few solitary pedunculated growths were only sparsely supported by connective tissue. Small areas of hemorrhage and necrosis were rarely observed, and there was little inflammatory reaction. Tumor cells occasionally extended into the perineural tissues and blood vessels. In 1 instance the main trunk of the portal vein was thrombosed. Fehr's case, not included in this study because the clinical history was lacking, is nevertheless interesting, for the neoplasm was constructed of tubules and strands of cylindric and low cuboidal cells together with large nests of epidermoid carcinoma growing independently or intermingled with the glandular cells. These nests consisted of squamous epithelial cells, often arranged concentrically and producing epithelial pearls.

CARCINOMA OF THE COMMON BILE DUCT

Included in this group are only those cases of carcinoma in which the tumor definitely originated in the common bile duct, between the orifice of the cystic duct and the ampulla of Vater and not involving either of these structures. The neoplasms arising in and about the papilla and ampulla of Vater have been considered in a previous communication (Lieber, Stewart and Lund). One new case of primary carcinoma of the common bile duct is reported. Eighty-six cases of this condition were abstracted from the literature, 20 of which were regarded as acceptable on the basis of a clinical history and gross and microscopic studies of the primary lesion.[10] Fifteen additional cases, although probably authentic, were not included because of lack of a clinical history or because of insufficient details.[11] Fifty-one cases were discarded for the following reasons: In 38 cases [12] no histologic examination of the primary lesion was reported, the diagnosis apparently being based on

10. Ormerod; Chappet; de la Camp, case 1; Griffon and Dartigues; Durand-Fardel; Devic and Gallavardin, case 1; Uliszewski, case 1; Borelius, cases 2 and 3; Morian, case 4; Leclerc; Bret and Dufourt; Petrén, cases 20 and 22; Dalla Valle, cases 1 and 3; Shapiro and Lifvendahl, case 10; Cabot, case 16261; Demel; Pángaro, case 1.

11. Birch-Hirschfeld, cases 1 and 2; Moore, case 1; Hebb; Rolleston, cases 10 and 11; Quensel and Vestberg; Gianelli; Saltykow, cases 2 and 4; Schüssler, case 4; Dalla Valle, case 2; Mosto, cases 1 and 2; and Shapiro and Lifvendahl, case 9.

12. Durand-Fardel; Segond; Delafield; Kraus; Herringham, case 18; Peck; Brenner, case 2; Pennato, case 2; Dobrovici and Faix; Arnsperger, case 26; Goldammer, cases 216, 218, 219 and 220; Schaffner; Stieda, case 14; Koerber, case 1; Schmidt, case 1; McGlinn, cases 1022A and 3037A; Paus, cases 211 and 215; Cheney; Zuccóla, case 1; Poynton; Petrén, case 1; Castex; Schüssler, case 2; Forgue, Roux and Milhaud; Dalla Valle, cases 4, 5, 6, 7, 8 and 9; Murgoci, case 2; Blomström, case 4; Bettoni, case 1.

gross inspection alone; in 13 cases [13] the ductal origin of the neoplasm was not established with certainty in the presence of involvement of the pancreas in 4, of the stomach in 3, of the gallbladder in 3, of the rectum in 2 and of the cecum in 1, since any of the organs may have been the primary source of carcinoma. Thus there is a total of 21 cases in this group.

CASE 6.—E. S., a white woman, was admitted to the Jefferson Hospital in 1912 for chronic nephritis, in 1928 for cataract, in 1929 for drainage of an abscess of the liver with partial cholecystectomy and cholecystostomy, in 1930 for an incisional hernia and multiple intestinal adhesions and in 1933 for ulcerative cystitis. Her last admission to the hospital, at the age of 76, was on July 26, 1934. There were loss of appetite, epigastric pain, jaundice, belching and abdominal tenderness of three months' duration. The pain was continuous and dull and did not radiate. Examination revealed obesity, marked jaundice and stupor. The abdomen was prominent and showed the scars of previous operations. The liver was palpable 4 fingerbreadths below the costal margin, in the midclavicular line, and was tender and smooth with rounded edges. The temperature varied from 97.2 to 100.4 F., with a sharp rise to 104.6 F. shortly before death. Roentgen examination was performed on two occasions and showed a walnut-sized shadow in the right upper abdominal quadrant, not definitely in the gallbladder and interpreted as a calcified mesenteric lymph node. Duodenal drainage on one occasion failed to yield bile. The hemoglobin content of the blood was 68 per cent; the red blood cell count was 3,500,000 and the white blood cell count 6,000 per cubic millimeter; the color index was 0.9; the bleeding time was three minutes, and the clotting time was four minutes. The Wassermann and Kahn reactions on the blood serum were negative. The nonprotein nitrogen content of the blood was 36.14 mg. and the sugar content 82 mg. per hundred cubic centimeters. A test of hepatic function with bromsulphalein showed 80 per cent retention of the dye at the end of thirty minutes (2 mg. dose). The reaction to the direct van den Bergh test was positive, and the value for serum bilirubin was 26 mg. per hundred cubic centimeters. The urine was variably acid and alkaline, with a specific gravity of 1.014 to 1.022, and contained a trace of albumin. The patient's course in the hospital was characterized by progressive increase of jaundice, repeated vomiting, increasing weakness and death on August 28.

Autopsy was performed seventeen hours after death. The combined gross and microscopic diagnoses were: (1) adenocarcinoma of the common bile duct, with extension to the pancreas and metastasis to a regional lymph node; (2) hydrohepatosis, with biliary cirrhosis and marked jaundice; (3) chronic cholecystitis and rupture of the gallbladder; (4) fatty infiltration of the pancreas, with fat necrosis; (5) extensive peritoneal adhesions; (6) marked generalized arteriosclerosis; (7) siderotic deposits in the capsule of the spleen; (8) fibrosis and fatty infiltration of the myocardium; (9) coronary occlusion; (10) chronic nephritis, and (11) bronchopneumonia.

There was an old healed scar in the right upper quadrant of the abdomen. The intra-abdominal structures were obscured by dense peritoneal adhesions extending between the liver, the gallbladder, adjacent portions of the gastro-

13. Van der Byl; Stiegele; Häni, case 7; Rousseau and Morin; Murchison; Van Gieson; Bernheim and Simon, case 1; Moschcowitz; Schönbauer and Bsteh, case 5; Secco and Pángaro; Shapiro and Lifvendahl, case 5; Nochimowski, case 3; Miodowski, case 5.

intestinal tract and the anterior abdominal wall. In an attempt to separate these adhesions a cystic area was broken into, which yielded a large quantity of thick, dark green granular fluid. The ampulla of Vater was patent and admitted both the pancreatic and the common bile duct, both of which were slightly dilated but emptied freely into the intestine. Two centimeters above the ampulla the common bile duct was tightly strictured by a thickened, indurated mass. At the point of involvement the lumen was not completely obliterated, for a small amount of dark green fluid could be forced past the obstruction by pressure on the ducts above

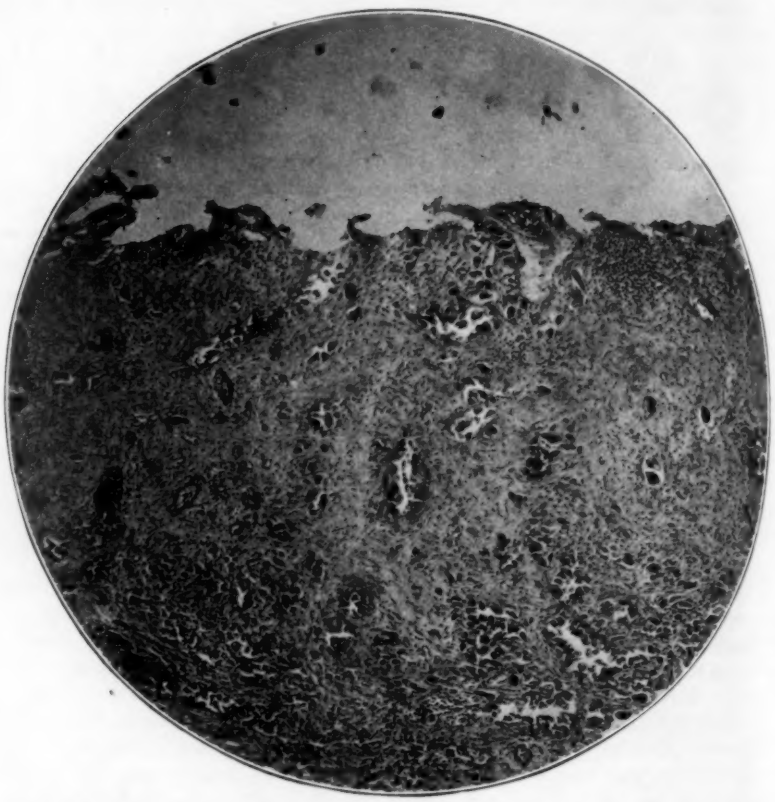

Fig. 6 (case 6).—Common bile duct, showing hypertrophied villi and neoplastic proliferation of tumor cells on the surface with permeation of the wall and deeper tissue. × 50.

after partial dissection of the specimen. A cross section through the point of constriction revealed a triangular, firm, nodular lesion 1 cm. on a side, embedded in the wall of the duct and in a portion of the underlying pancreas. The pancreas elsewhere showed extensive fatty infiltration and small areas of pancreatic necrosis. Proximal to the constriction the bile ducts were markedly dilated, the cystic duct readily admitting the passage of a probe. The fundus of the gallbladder was torn away, and the portion of the wall remaining was continuous with the large encysted area broken into as described. This cavity was walled in by the posterior surface

of the liver, the anterior wall of the colon, portions of the pancreas and duodenum and dense surrounding adhesions. No gallstones were found.

The liver was bile stained, soft, cystic and mottled with dark green areas intermingled with yellowish ones. On section of the liver little bile was found in the ducts, and there was a moderate increase in connective tissue. Apparently most of the bile had entered the cyst which enclosed the ruptured gallbladder.

The duodenum and the first portion of the jejunum contained a small amount of dark granular fluid. The feces were clay colored. Several lymph nodes about the common bile duct and pancreas were enlarged, soft and pigmented.

Microscopically the entire wall of the common bile duct at the point of obstruction and the underlying pancreas were involved by tumor growth over a triangular area measuring 1 cm. on a side. On the surface of the duct the villi were hypertrophied owing to the presence of atypical epithelial cells (fig. 6). The hypertrophied villi were separated by deep fissures. Elsewhere on the surface the epithelium was autolyzed. The tumor cells were essentially columnar, but some appeared round and elongated. Their nuclei were relatively large, hyperchromatic and irregular but rarely multiple; none were observed in mitosis. The cytoplasm was acidophilic and frequently showed one or more large vacuoles containing stringy mucin. The tumor cells were arranged chiefly in the form of acini of various sizes, many of them relatively large, or as clumps and strands. The stroma was abundant and contained a few inflammatory foci. Pancreatic permeation occurred chiefly in the interstitial tissue, with consequent atrophy of the parenchyma and perilobular fibrosis.

Small metastatic deposits were present in the cortical sinuses and afferent lymphatic vessels of one of the regional lymph nodes. The gallbladder was markedly thickened and fibrotic, with atrophy of the musculature and a diffuse inflammatory cell reaction; the epithelial lining was autolyzed. At the fundus, along the line of rupture, there was a wide zone of necrosis extending through the entire wall of the gallbladder, causing fragmentation and wide separation of tissue fibers, between which there was a deposit of brown pigment. The liver showed autolysis, marked biliary pigmentation, moderate fibrosis and inflammatory cell infiltration in the portal areas. Several small abscesses were present in the parenchyma. The kidneys showed marked biliary pigmentation. Siderotic nodules (Gamna-Gandi bodies) were present beneath the capsule of the spleen.

AGE AND SEX INCIDENCE

Twelve patients were men varying in age from 48 to 76 years, with an average of 60, and 9 were women varying in age from 42 to 76 years, with an average age of 60.

It was impossible to estimate accurately the incidence of proved primary carcinoma of the common bile duct exclusive of the ampulla of Vater and the duodenum, which of course are frequently invaded secondarily by tumors of the common duct. Many of the neoplasms considered in a previous communication on primary carcinoma of the peripapillary portion of the duodenum (Lieber, Stewart and Lund) may actually have arisen from the lower portion of the common bile duct. However, as was set forth in that publication, it was not possible absolutely to eliminate their origin from neighboring structures, such

as the pancreatic duct, the ampulla of Vater or the duodenal mucous membrane covering the papilla of Vater. Therefore, the true incidence of primary carcinoma of the common bile duct must remain in doubt pending publication of statistical data which rest on carefully worked up material. The new case reported here occurred among 3,526 autopsies performed at the Jefferson Hospital (0.028 per cent of all autopsies).

MORBID ANATOMY

The location of the neoplasm could be accurately determined in 17 cases. In 7 it was localized in the lower end of the common bile duct, and in the remaining 10 the incidence was equally divided between the middle and upper segments; the exact situation of tumor in the other cases was not stated. However, it was perfectly clear that in all 21 cases there was complete absence of neoplastic involvement of the ampulla of Vater and the duodenal mucous membrane below and of the hepatic and cystic ducts above. The neoplasm formed a localized growth in 12 cases, varying in size from a few millimeters to the size of a pea, a cherry seed or a walnut, the largest growth being the size of a hen's egg. The tumors were soft; they were gray, yellow or white, with a granular papillary surface. In 1 case, 8 to 10 cm. of the common bile duct was involved by multiple soft, vegetating nodules between which the mucosa was thickened and hyperemic but not ulcerated. In 9 cases the neoplasm formed a diffuse, firm stenosing growth, granular and vegetating on the surface. There was ulceration in 6 cases, the ulcer being microscopic in 2, while in another it eroded deeply the wall of the bile duct into the head of the pancreas. With both the local and the diffuse types the wall of the duct was usually thickened as much as 1 cm.

Occlusion of the duct was complete in 11 cases; in the remainder no statement regarding the degree of obstruction was made. Proximal to the obstruction, the biliary ducts were maximally dilated.

Extension or metastases or both occurred in 11 cases, as follows: in the liver (6 cases); in the regional lymph nodes (5 cases); in the lungs (3 cases), and in the gallbladder (1 case). In 1 case, metastatic deposits were confined to a single lymph node above the left clavicle. In several cases only one or two regional lymph nodes contained metastatic deposits. The secondary growths in the liver were frequently multiple, but in 1 case there was an enormous solitary mass replacing a large portion of the organ. Extension of the primary process into the pancreas occurred in 4 cases, in 3 of which metastases were not present elsewhere. The infiltrating lesions were small in all instances, replacing a portion of the immediately underlying pancreas and invading vessels and nerves in 3 cases, while in the fourth an ulcerative lesion in the common duct also extended deeply into this organ.

The features of biliary stasis were present in all cases in which the liver was described, and some degree of cirrhosis was also present in 5 cases. In all but a single instance (to be noted) the gallbladder was distended or was not described. The contents of the gallbladder were clear and colorless in 6 cases and green, tarry and purulent in 1 case each. Biliary calculi were present in the gallbladder in 6 cases, in 1 of which the common bile duct also harbored a calculus. Marked cholecystitis was noted in 2 cases, and in 2 others the wall of the gallbladder was thickened. In our case in which the gallbladder had ruptured, the fundus was torn away, and what remained of the wall of the viscus was continuous with a large encysted area walled in by dense adhesions to the posterior surface of the liver, the anterior wall of the colon and portions of the pancreas and the duodenum. A considerable quantity of dark green granular fluid was contained in the cyst, with little bile remaining in the intrahepatic biliary passages. The pancreas, aside from neoplastic infiltration in 4 cases, showed relatively little change. There was slight pancreatic fibrosis in 4 cases and areas of fat necrosis in another. Obstruction of the pancreatic ducts was not described in any case in this series.

Peritoneal effusions occurred in 6 cases, the fluid being icteric in 4 and hemorrhagic in 2, in 1 of which the effusion followed laparotomy. A total of approximately 30 liters of icteric fluid was drained off by paracentesis on three occasions from a patient with continuous jaundice of eight month's duration. Pericholecystic adhesions were present in 7 cases (to the primary tumor, the duodenum, the stomach, the colon, the inferior and posterior surfaces of the liver and the anterior abdominal wall).

HISTOLOGIC PICTURE

The tumors in all but 1 of the cases in this series were glandular carcinomas, the exception being a squamous cell carcinoma (Cabot, case 16261). In 1 case carcinoma simplex was designated. Acini were present in the remainder and tended to uniformity in size, although some were anastomotic, with papillary spurs in 1 instance. Many atypical cells grew in the form of clumps or strands. The cells were essentially cylindric, columnar or cuboidal but varied considerably in size, shape and staining in many cases, pleomorphism being a marked feature in 3. Mitotic figures were observed in a single case, and multiple nuclei were noted in 2 others. The cells were generally well preserved, and little necrosis was evident. There was usually an abundant stroma, which was sparse in only a single instance.

The zone of malignant transformation as described in a few cases consisted of atypical epithelial cells several layers thick, eventuating in

the development of granular papillomatous formations or a solitary excresence on the surface of the common duct. Chappet stated that the cancer in his case arose from the depths of the mucosa in the form of large alveoli which grew toward the lumen of the duct; the other layers of the duct were invaded with comparatively few cylindricocuboidal new formations in the submucosa. Devic and Gallavardin's case illustrates a tendency for the neoplasm to remain localized to the duct, which was thickened, ulcerated and lined by epithelial vegetations, sharply separated, however, from the underlying pancreas by a thick band of connective tissue.

CLINICAL FEATURES

The clinical features of carcinoma of the extrahepatic bile ducts are based on a consideration of 104 cases, as follows: 35 cases of tumor primary in the hepatic duct; 48 of tumor primary at the confluence of the hepatic, cystic and common bile ducts, and 21 of tumor primary in the common bile duct. Since the symptoms and physical findings did not vary significantly with the point of involvement, this phase of the study is dealt with under one heading. Any clinical deviations dependent on the situation of the neoplasm as outlined in the section on morbid anatomy are indicated.

Onset.—The onset was acute in 92 cases and gradual in 12. The symptoms occurring with the acute onset were jaundice (51 cases), pain (37 cases), pruritus (15 cases), loss of weight and strength (13 cases), vomiting (11 cases), anorexia (10 cases), fever (9 cases), diarrhea (7 cases), constipation (6 cases), nausea (5 cases) and (infrequently) chills, a sense of weight or pressure in the abdomen, flatulency and belching. Symptoms occurring after the onset were loss of weight and strength (48 cases), jaundice (41 cases), pruritus (19 cases), fever (13 cases), anorexia (12 cases), diarrhea (12 cases), pain (10 cases), constipation (9 cases), abdominal distention (5 cases), nausea (5 cases), vomiting (4 cases) and (infrequently) chills, a sense of weight or pressure in the abdomen, flatulency and belching.

Symptoms coinciding with the gradual onset were anorexia (6 cases), loss of weight and strength (5 cases), pain (4 cases), a sense of weight or pressure in the abdomen (3 cases), indefinite abdominal symptoms (3 cases), diarrhea (3 cases), nausea (2 cases), and vomiting and fever (1 case each). Later symptoms were jaundice (12 cases), vomiting (7 cases), loss of weight and strength (4 cases), pain (4 cases), fever (4 cases) and nausea, anorexia, chills and constipation (1 case each).

A history of an antecedent illness was elicited in 11 cases in which the onset was acute and in 1 case in which it was gradual. In the last-mentioned case long periods of pain and diarrhea antedated the gradual

onset by two years. In the first-mentioned group, variably brief attacks of pain, either single or multiple, were noted in 7 cases and preceded the onset of the present condition by one to five years. Of the remaining 4 cases, there were distention and discomfort after meals for five years in 1, long periods of diarrhea in 1, protracted, alternating diarrhea and constipation in 1 and pulmonary tuberculosis of two years' standing in the fourth.

Jaundice.—This sign was present in all patients at some time during the course of the illness. Jaundice occurred at the onset in 51 cases and later in 53. With carcinoma of the hepatic and common bile ducts jaundice occurred equally early and late, but with carcinoma of the confluence of the three ducts a majority of patients exhibited jaundice later, in about the proportion of 5 to 3. In the group of cases in which jaundice occurred later the interval from the first appearance of symptoms to the onset of jaundice varied from a few days to eighteen months, averaging one and a half to two months except in the group with cancer of the hepatic duct, in which the average was about three months.

There was a single attack of jaundice in 90 cases, and, although variations in intensity occurred in all but 10 of these, an icteric tint was always present unless operation was resorted to. In Bret and Dufourt's case icterus was present without appreciable variation in intensity for eleven months. The duration of jaundice in 83 of the 90 cases varied from a few days to twenty-three months, averaging about three and one-half months. Jaundice was present for less than a month in 13 cases, for one month in 14, for two months in 13, for three months in 8, for four months in 11, for five months in 6, for six to twelve months in 17 and for twenty-three months in 1. There were two attacks of jaundice in 5 cases, and in the remainder the number of attacks was not stated. In the group with multiple attacks the duration of jaundice varied from a few days to five months, and the interval between attacks, from one week to one month. The sum of the duration of each individual attack of jaundice plus the interval between in 9 cases of this group varied from four to eighteen months, giving an average total duration of eight and one-half months.

Jaundice occurred as the sole sign in 13 cases and in association with loss of weight and strength only in 14; with diarrhea only in 4, and with fever only in 1. The relation of jaundice to the other commonly occurring symptoms is of interest. Jaundice was preceded by pain in 32 cases, by nausea or vomiting or both in 16, by anorexia in 14, by loss of weight and strength in 10 and by fever, sometimes with chills, in 5. Jaundice occurred simultaneously with pain in 10 cases, with loss

of weight and strength in 8, with nausea or vomiting or both in 5, with fever in 5 and with anorexia in 5. The appearance of jaundice was followed by loss of weight and strength in 52 cases, by fever in 17, by anorexia in 9, by pain in 13 and by nausea or vomiting or both in 6.

Pain.—Pain was present in 55 cases, absent in 24 and not mentioned in the remainder. It occurred with the onset of the condition in 41 cases and later in 14. Pain was localized in the epigastrium or the right side of the hypochondrium or both in 36 cases, and in the back or the lumbar region in 2; in 1 case each it was present diffusely over the abdomen, in the left side of the abdomen and in the right flank. Pain radiated to the back in 5 cases, to the shoulders or the midscapular region in 3 and down both arms in 1. In another case, pain commenced in the left shoulder and radiated to the midthorax, the left side of the hypochondrium, the epigastrium and finally the right side of the hypochondrium. Pain was described as severe in 14 cases, colicky or cramp-like in 5, dull in 8 and vague in 3. It was intermittent in 24 cases and unremitting terminally in 5. A relation between food and pain existed in only 5 cases; of these, pain, heaviness or a sensation of pressure followed ingestion of food in all, continuing all night in 1. Nocturnal pain was a feature in an additional case. In another case a sensation of pressure in the epigastrium before meals became accentuated after eating.

Nausea and Vomiting.—Vomiting was present in 23 cases, absent in 25 and not mentioned in the remainder. Vomiting occurred with the onset in 12 cases and later in 11. Nausea was complained of in 4 cases in which vomiting was not a symptom. Vomiting was intermittent and was never a distressing symptom. It was related to food in only 1 case, in which it sometimes followed ingestion of coarse food.

Examination of aspirated gastric contents was made in 9 cases, in 1 of which the material was reported as normal. In the others free hydrochloric acid was absent in 6 cases, reported as 13 in one and not mentioned in another. The total acidity in 6 cases varied from 10 to 31, with an average of 19. Lactic acid was present in 4 cases and absent in 2. Occult blood was present in 1 case. Duodenal drainage was performed in 5 cases. In Pángaro's case of carcinoma of the common bile duct without involvement of the duct of Wirsung, the duodenal fluid was clear and acid and contained bile but no pancreatic ferments. In Romano and Rey's case, in which bilirubin and pancreatic ferments were not found, autopsy revealed a carcinoma of the confluence of the bile ducts, but no mention was made of the pancreatic ducts. In Pérez Fontana, Anastasia and Castro's case of carcinoma of the hepatic duct, repeated duodenal drainages were performed, and the fluid obtained

was always colorless. In Quénu and Gasne's case of carcinoma of the confluence of the bile ducts, the duodenal fluid on two occasions was slightly alkaline and contained bile pigments and a few pus cells but no blood. In our case 6, bile was absent from the duodenal contents.

Diarrhea and Constipation.—Diarrhea occurred early in 10 cases and late in 12, while constipation occurred early in 6 and late in 9. Alternating diarrhea and constipation were manifested in 3 cases.

The stools were colorless, gray or clay colored in 56 cases, light brown in 1, slightly bile stained in another and not described in the remainder. In 2 cases the stools varied at times from normal to colorless. Blood was detected in 9 stools examined and absent in 6. Bile was present intermittently in 3 cases. The stools were occasionally fetid and contained an excess of fat in 8 cases.

PHYSICAL EXAMINATION

Abdominal masses representing the primary growth were not detected clinically in any case in this series. The liver was enlarged in 71 cases, in 3 of which it was nodular; it was not enlarged in 8 cases. The gallbladder was palpable in 27 cases and not palpable in 19. Abdominal tenderness was elicited in 26 cases, with associated rigidity in 3. Abdominal distention developed in 11 cases, usually late, and evidences of ascites were recorded in 8 cases. The spleen was enlarged and tender in 3 cases. In 1 case there was palpable enlargement of a lymph node in the left supraclavicular fossa.

OTHER LABORATORY DATA

Studies of the Blood.—Studies were made in 26 cases. A varying grade of anemia was present in 17, the red blood cells varying from 2,300,000 to 3,850,000 per cubic millimeter in 13 cases, with only 910,000 red cells and a 15 per cent concentration of hemoglobin in 1 case. The values for hemoglobin varied from 15 to 85 per cent in 10 cases, in 4 of which the color index was high (1.02, 1.05, 1.18 and 1.37). In 1 case the red blood cell count and the hemoglobin level were normal. Slight leukocytosis was present in 4 cases, and in 2 the white cell counts were 25,000 and 30,000 per cubic millimeter respectively. The bleeding and coagulation times were estimated in 11 cases. The bleeding time was normal in all; there was prolongation of the coagulation time from twelve to twenty minutes in 4 cases. The van den Bergh estimations on the blood serum varied from 6.4 to 34 mg. per hundred cubic centimeters in 4 cases, with an average of about 22 mg. The icterus index varied from 30 to 150 in 6 determinations, with 92 as an average. In 3 patients so examined tests of hepatic function with bromsulphalein

showed varying impairment, with 40 to 100 per cent retention of the dye in thirty minutes (2 mg. dose). The value for blood sugar was within normal limits in 11 cases and increased to 200 mg. in 1 case. Retention of nitrogenous products in the blood occurred in 4 cases.

Urinalysis.—During icteric phases the urine was deep amber, green or dark brown, and bile was detected in every case in which a test for it was performed. Albumin in traces was detected in 12 cases and in large amounts in another. The urine contained sugar in 7 cases, in 1 of which the patient was treated daily with intravenous injections of dextrose solution. Urobilin was present in the urine in 9 cases and absent in 3. Casts, red cells, leukocytes and albumin suggested severe renal impairment in a few cases.

Roentgen Examination.—Roentgen studies were carried out in 22 cases. In 8 cases, a simple flat plate of the abdomen was made. In 7 cases, examination of the gastrointestinal tract after a barium sulfate meal was reported as revealing no abnormality except diverticulosis of the colon in 1 case and cecal stasis in another. Positive findings were recorded in 6 cases of carcinoma of the confluence of the bile ducts and in 1 case of carcinoma of the hepatic duct. A brief analysis of these cases follow.

In Cabot's case 21,122 there were a hernia of the stomach and a diverticulum of the duodenal loop in the region of the gallbladder; at autopsy, a small tumor 1 cm. in length obstructed the common bile duct at the orifice of the cystic duct, and the roentgen picture was not accounted for by gross examination. In Lee and Totten's case 1, rapid emptying of the stomach and duodenum suggested extrinsic irritation; at autopsy, a stricture of the common duct extended from 1.5 cm. above to 0.5 cm. below the orifice of the cystic duct. In McLaughlin's case 2 the roentgenograms were interpreted as indicating malignant disease of the stomach; at autopsy, the stomach and duodenum appeared normal, but the hepatic and common bile ducts were involved by new growth. In Kurths's case, the right half of the diaphragm was immovable, and an extragastric tumor was suggested from the roentgen studies; autopsy revealed a nodule the size of a cherry seed obstructing the ducts at the confluence. In Wahl's case 5, partial stenosis of the pylorus due to adhesions to the gallbladder was suggested, but autopsy revealed that the stomach and intestines were normal and that there were no adhesions about the gallbladder; an indurated mass 2 to 3 cm. in length involved the cystic, common hepatic and common bile ducts. In Prat's case 2, gaseous dilatation of the intestines and adhesions between the stomach and the liver were suggested; at laparotomy, however, the stomach and intestines showed no visible change, and there were no adhesions but

instead a firm, nodular, indurated mass at the confluence of the bile ducts. In our case 3 there was a filling defect of the gastric antrum, with irregularity of outline, displacement, fixation and retention. Autopsy disclosed a soft, white nodule the size of a walnut in the hepatic duct, which merged with a larger mass in the liver.

The gallbladder was visualized in 1 case and not visualized in 5. An enlarged aorta, several large gallstones and a calcareous lymph node in the upper part of the abdomen were noted in 1 case each.

DIAGNOSIS

A correct provisional diagnosis was made clinically in 20 cases in which neoplastic obstruction of the bile ducts was suspected. In 33 cases one or more of the following diagnoses were made; carcinoma of the head of the pancreas (17 cases); carcinoma of the stomach (5 cases); calculous obstruction of the common bile duct (5 cases); carcinoma of the liver (3 cases); hypertrophic cirrhosis of the liver (3 cases), and carcinoma of the duodenum, carcinoma of the gallbladder, carcinoma of the colon, carcinoma of the prostate with hepatic metastases, obstructive jaundice due to malignant tumor, obstructive jaundice of undetermined origin, hemochromatosis, cholecystitis, angiocholitis and obstruction of the common bile duct by a plug of mucus (1 case each).

A correct surgical diagnosis of carcinoma of the hepatic duct, carcinoma of the confluence of the hepatic, cystic and common bile ducts or carcinoma of the common bile duct was made in 18 of 50 cases in which celiotomy was done. In 6 of these cases the lesion was localized in the region of the porta hepatis, or hilus of the liver. In 5 cases the primary lesion was mistaken for a benign fibrous stricture. One of the following diagnoses was made in each of 7 cases: stone in the hepatic duct, stones in the common bile duct, calculous cholecystitis, an indefinite mass behind the duodenum obstructing the bile ducts, tumor in the region of the pancreas, carcinoma of the papilla of Vater and metastatic tumor in the liver and omentum.

TREATMENT

The treatment of primary carcinoma of the extrahepatic bile ducts has been symptomatic, palliative or directed toward total eradication. The operative procedures, surgical results and pathologic observations differ widely, depending on the point of obstruction; hence the following group analysis is presented.

Carcinoma of the Hepatic Duct.—Fourteen patients were treated symptomatically only, and 12 lived for two to twenty-three months after onset, with an average of eight and eight-tenths months. In 2 cases the duration of illness was not recorded.

Celiotomy was performed in 21 cases, and the operative procedures and results are indicated in table 1. A summary of the surgical pathologic features of these cases follows. A lesion in the region of

TABLE 1.—*Results in Cases of Carcinoma of the Hepatic Ducts in Which Operation Was Performed*

Year	Author	Operation	Result
1893	Hesper, case 2.....	6/28/92 exploratory operation	Patient died 8 days after first operation
		6/30/92 cholecystostomy	Patient died 6 days after second operation
1898	Schuchardt.....	6/6/98 exploratory operation	Patient died 2 months after first operation
		7/6/98 choledochotomy	Patient died 1 month after second operation
1902	Ingelrans.....	Cholecystostomy	Patient died 19 days after operation
1904	Porot.....	Exploratory operation	Patient died 7 days after operation
1906	Houssin.....	Cholecystostomy	Patient died 20 days after operation
1907	Lapointe, Raymond and Merle	Exploratory operation	Patient died 2 days after operation
1908	Adlercreutz.....	Drainage of hepatic duct	Patient died several hours after operation
1910	Gutowitz.....	Cholecystectomy	Patient died 6 days after operation
1918	Petrén: Case 14.....	Drainage of hepatic duct	Patient died 1 month after operation
	Case 16.....	Cholecystectomy	Patient died 1 day after operation
1924	Wahl, case 4.....	Exploratory operation	Patient died 1 day after operation
1931	Bosco.....	Exploratory operation	Patient died several hours after operation
1932	Milles and Koucky...	Dilatation of stricture; removal of biopsy specimen; hepaticodudenostomy	Patient died 4 days after operation
1932	David: Case 1.....	Cholecystectomy; drainage of hepatic duct	Patient died 8 days after operation
	Case 2.....	7/?/28 cholecystectomy; choledochostomy 2/7/29	Patient died 8 months after first operation, patient died 30 days after second operation
1933	McLaughlin, case 4..	Cholecystogastrostomy	Patient died 9 days after operation; uremia, hemorrhage
1934	Lampert and McFetridge	Cholecystostomy	Patient died 14 days after operation
1934	Pérez Fontana, Anastasia and Castro, case 1	Cholecystoenterostomy	Patient died 5 days after operation
1935	Hess and Faltitschek, case 2	Exploratory operation	Patient died 1 day after operation
1935	Walters and Olson...	Excision; biopsy; insertion of 10 mg. radium of 14 hours	Patient living 4½ months after first operation
		One month later, excision of metastatic tumor on back	Patient living 3½ months after second operation
1939	Stewart, Lieber and Morgan	Cholecystostomy	Patient died 1 day after operation

the biliary ducts was detected by external palpation in 16 cases. The process was interpreted as a chronic inflammatory stricture in 3 of these cases and as an indurated lymph node in 2; in 5 cases, the local indurated lesion was thought to be an embedded stone, but in each of these incision of the bile ducts revealed the neoplastic process. In 6 remaining cases the tumor was unrecognized until autopsy was performed. The surgical

pathologic picture of these cases is interesting. The primary growths were all localized and small, ranging from the size of a pea to that of a walnut. Metastases in the regional lymph nodes were present in 3 cases. Peritoneal effusions of icteric fluid occurred in 3 cases and of bloody fluid in 1. The liver was usually enlarged and jaundiced. The gallbladder was distended in 5 cases, with white bile in 1 and blood-stained fluid in another; it was normal in size or not distended in 4 cases, being filled with thick mucopurulent material in 2 and thin icteric fluid in another. The gallbladder was collapsed and empty in 4 cases and contracted in 3, in 1 of which it embraced a large stone; another was adherent to the duodenum. No mention of the size of the gall-bladder was made in the other cases, although calculi were present in 2 of these, in 1 of which stones were also present in the cystic duct. Variability in size of the gallbladder in this group of cancers of the hepatic duct requires emphasis and is to be contrasted with the picture in cases of carcinomatous obstruction at or below the terminal orifice of the cystic duct. In these cases cholecystic distention regularly takes place unless the gallbladder was previously diseased.

The clinical state of the patient after operation was commented on in only 5 cases. In Schuchardt's case, exploratory celiotomy was first performed, followed by choledochotomy a month later; jaundice remained as intense as before, and pain continued unabated, although the feces regained a slightly brown color. In Petrén's case 14, drainage of the hepatic duct was followed several days later by bile staining of the secretions, and bile appeared in the feces eighteen days later. In David's case 2, after cholecystectomy and drainage of the common bile duct, jaundice gradually declined but reappeared, associated with pain, six months later, at which time the hepatic duct was found obstructed by a firm, fibrous thickening the size of the tip of the thumb. In Lampert and McFetridge's case, a cholecystostomy was performed two weeks before death, which, of course, did not relieve the bile stasis, as this was due to obstruction higher in the hepatic duct, and therefore jaundice failed to abate. In McLaughlin's case 4, cholecystogastrostomy was performed. The patient became practically anuric on the eighth day, the little urine obtained showing a cloud of albumin and large granular casts. Chemical examination of the blood showed the value for urea nitrogen to be 80 mg. and that for creatinine to be 2.45 mg. per hundred cubic centimeters; these values rose to 97 mg. and 3.06 mg. respectively on the following day. The patient died on the tenth postoperative day, after passing dark blood by bowel and vomiting 1,000 cc. of dark blood. This case is probably illustrative of the hepatorenal syndrome, which in certain instances, at least, appears to have a morphologic basis (Lieber and Stewart). The liver in this case showed diffuse fibrosis and

extreme acute degeneration also resembling that described by us for patients subjected to surgical procedures on the gallbladder (Stewart and Lieber).

There was an ultimate mortality rate of 100 per cent in this series of carcinoma of the hepatic ducts. The total survival period from onset to death varied from one week to twelve months, averaging six and forty-eight hundredths months. The average postoperative survival period was nine-tenths month. Fourteen patients died during the first fourteen postoperative days, and 1 each on the nineteenth and twentieth days. The exact postoperative duration of survival was not recorded in 1 case, in which, however, there were extensive metastases one month after operation. Survival periods of one, two and eight months respectively were recorded in each of 3 cases, and in another, despite metastases, the patient was still alive four and a half months after operation. Of the 21 cases just enumerated, 2 deserve special mention. David's case 2 is of interest because of an eight month period of postoperative survival. At the first celiotomy, although no lesion was encountered, the gallbladder was removed and the common bile duct drained, and these operations, curiously enough, were attended by disappearance of jaundice. With recurrence of symptoms, a second celiotomy was performed seven months later, at which time an obstruction was found in the hepatic duct. Again the common bile duct was simply drained. The patient died five weeks later, eight months after the first operation. Obviously the operative procedures instituted in this case can be considered as having had little or nothing to do with disappearance of symptoms or with prolonging the life of the patient. Spontaneous regression of symptoms occurs sometimes in patients with cancer of the bile duct who are not subjected to surgical procedures. Certainly nothing effective was done in the case just cited to relieve the obstruction causing jaundice. The disappearance of jaundice under these circumstances must, therefore, be regarded as purely coincidental. Walters and Olson's case is particularly interesting, for it was the only one in which complete eradication of the neoplasm was attempted. At celiotomy in their case the common bile duct was found dilated and filled with masses of mucoid material, which were removed. In the region of the bifurcation of the hepatic duct a papillary lesion was located, with a pedicle about 1.5 cm. in diameter. This soft tumor was broken up, only a small portion of pedicle being left attached to the wall of the duct. Two radium needles (5 mg. each) were then placed in the duct for fourteen hours, after which the common duct was closed over a T tube. One month later, a mass 7 by 5 cm. presented itself posteriorly between the ninth and eleventh ribs. This gradually increased in size, and at the end of three weeks it was incised and drained, yielding a pint of

gelatinous material. The mass recurred, and still another nodule, 3 cm. in diameter, appeared in the abdominal wall. The patient was last seen four and a half months after the first operation, and no record of his subsequent fate was available.

A comparison of the average total survival periods of the surgically treated patients (six and forty-eight hundredths months) and those treated medically (eight and eight-tenths months) gives the latter a slightly more favorable margin. The high immediate postoperative mortality rate, amounting to about 76 per cent, is largely responsible for this difference. Thus the increase in life expectancy which was accomplished in a few instances by surgical methods is completely nullified by the high immediate postoperative mortality. The favorable results obtained in a few instances, however, encourage early diagnosis, early operation and more detailed study of cases. The tumors are small, and slowly growing and metastasize late. When they are situated low in the common hepatic duct, excision with reestablishment of biliary flow may be feasible. A tumor at the upper end of the common hepatic duct frequently involves one or both branches of the duct, sometimes with direct spread into the liver and the nearby structures. The difficulties of instituting any sort of effective treatment under these circumstances can readily be appreciated.

Carcinoma of the Confluence of the Ducts.—Twenty-seven patients were treated medically, and 26 of these lived for from one to eight months after onset, averaging four and six-tenths months; in the other case the duration of survival was not stated.

Celiotomy was performed on 21 patients, and the operative procedures and results are indicated in table 2. A consideration of the surgical pathologic picture in these cases follows. The primary neoplasm was correctly detected by direct palpation through the open abdomen in most instances; in 2, however, a localized growth was mistaken for a biliary calculus, and in another a more diffuse lesion was regarded as a benign fibrous stricture. The primary neoplasm varied in size from that of a cherry to that of a hazelnut. Metastases were encountered in only 2 cases. The liver was regularly enlarged and jaundiced. The gallbladder was frequently distended with clear, colorless fluid. However, it was small and thin walled in 4 cases and atrophied and thickened in another; in the last-mentioned case it contained many stones and a small quantity of purulent fluid. Gallstones were present in the gallbladder in 3 cases and in the cystic duct in 1. The hepatic ducts proximal to the obstructing neoplasm were dilated frequently with clear, colorless fluid.

There was an ultimate mortality rate of 100 per cent in this group. Thirteen patients died during the first fourteen postoperative days, and 1 died one and one-half months after operation. Seven patients, how-

ever, survived for three, four, six, eleven, twelve, seventeen and twenty-seven months respectively, averaging about eleven and five-tenths months after operation. Their cases deserve individual mention. At

TABLE 2.—*Results in Cases of Carcinoma of the Confluence of the Hepatic, Cystic and Common Bile Ducts in Which Operation was Performed*

Year	Author	Operation	Result
1899	Brenner, case 1.....	8/24/98 partial cholecystectomy; cholecystostomy	Patient died 3 months after first operation
		9/30/98 cholecystoenterostomy	Patient died 1½ months after second operation
		11/?/98 choledochoenterostomy	Patient died ? months after third operation
1901	Lecène and Pagniez, case 1	Exploratory operation	Patient died 1 day after operation
1902	Uliszewski, case 2....	Cholecystostomy	Patient died 9 days after operation; hemorrhage
1902	Miodowski, case 6....	Cholecystoenterostomy	Patient died 7 days after operation
1903	Kehr.....	Resection; cholecystectomy; hepaticoduodenostomy	Patient died 27 months after operation
1904	Donati.....	Cholecystostomy	Patient died 1½ months after operation
1905	Weber and Michels...	10/7/04 exploratory operation	Patient died 4½ months after operation
		12/13/04 intrahepatic cholangiostomy	Patient died 2 months after second operation
1908	Borelius, case 1.....	Exploratory operation	Patient died 4 days after operation
1911	Spindler.....	Resection; cholecystectomy; reconstruction of common and hepatic ducts	Patient died 7 days after operation
1912	Lameris.....	11/23/07 resection; cholecystectomy; drainage of hepatic duct	Patient died 17 months after first operation
		8/27/08 resection of recurrent lesion; partial excision of liver; drainage of hepatic duct	Patient died 8 months ofter second operation
1921	Pallin, case 4.....	Resection; hepaticoduodenostomy	Patient died 11 months after operation
1923	Prat, case 2.....	Resection; hepaticoduodenostomy	Patient died several hours after operation
1928	Vander Veer and Nellus	Cholecystostomy	Patient died 4 days after operation
1928	Pliverić.....	Resection	Patient died 10 days after operation
1929	Carnot.....	Choledochotomy; biopsy	Patient died 3 days after operation
1931	Mondor.....	Hepaticogastrostomy	Patient died 6 months after operation
1933	McLaughlin, case 3..	Exploratory operation	Patient died 5 days after operation
1934	Lee and Totten, case 1	Dilatation of stricture and catheter inserted to restore lumen of hepatic and common bile ducts	Patient died 7 days after operation; hemorrhage
1935	Romano and Rey, case 1	Cholecystostomy	Patient died ? days after operation
1936	Quénu and Gasne....	Resection; hepaticoduodenostomy	Patient died 12 months after operation
1937	Cabot, case 22492....	Removal of biopsy specimen	Patient died 4 days after operation

celiotomy in Kehr's case a round, hard hazelnut-sized tumor was palpated at the bifurcation of the cystic and hepatic ducts, and a stone of about equal size was embedded in the cystic duct. The gallbladder,

the cystic duct, 1.5 cm. of the proximal portion of the common bile duct and 2 cm. of the lower portion of the common hepatic duct were excised, and the stump of the last-mentioned structure was then implanted into the duodenum. No notes as to the immediate subsequent clinical course of the patient were recorded, but death twenty-seven months later was attributed to abscesses of the liver. At the first celiotomy in Lameris' case, a walnut-sized tumor at the confluence of the ducts was excised, and a cholecystectomy was performed, together with drainage of the hepatic duct. The symptoms gradually disappeared, and the patient regained his previous good health for nine months, after which, at the second celiotomy, a recurrent tumor the size of a hen's egg was found partly in the liver and partly in the hepatoduodenal ligament. To remove the tumor it was necessary to excise a portion (6 by 2.5 cm.) of the right lobe of the liver. The jejunum was brought up and anastomosed to the hepatic wound, and a drain was inserted into the remnant of the hepatic duct. The patient was again free from symptoms for about five and one-half months and then complained of loss of weight and slight fever and died seventeen months after the first operation, eight months after the second operation. At autopsy there were metastases and numerous abscesses in both lobes of the liver. The jejunum when opened showed ten small openings on the mucosa, from which a rather large quantity of greenish yellow bile was expressed by applying pressure to the liver. Microscopically these openings proved to be newly formed biliary ducts from the liver which were functioning satisfactorily eight months after hepatointestinal anastomosis. In Quénu and Gasne's case, a hazelnut-sized tumor at the confluence of the ducts was excised, and the hepatic duct was implanted in the duodenum. The feces acquired bile staining in twenty days, and icterus finally disappeared completely. No further record of the patient's condition was made until death, twelve months after celiotomy, and unfortunately no autopsy was performed. In Pallin's case a tumor 2 cm. long at the confluence of the ducts was excised, and the stump of the hepatic duct was anastomosed to the duodenum. The patient remained in good health for nine months; then epigastric pain developed, together with recurrent chills and fever, followed by increasing jaundice. Death occurred eleven months after celiotomy, and autopsy revealed suppurative cholangitis with multiple hepatic abscesses. Since no remains of the cancer were detected at autopsy, this patient might be regarded as potentially cured of the neoplasm, although death was due to its secondary effects. However, the survival period of nine months was too short to make this a conclusive cure of cancer. Celiotomy in Mondor's case revealed an olive-sized mass at the confluence of the ducts, and the hepatic duct was anastomosed to the stomach. All symptoms gradually disappeared coincidentally with a gain of 10 Kg. in weight in five months. The

patient then had increasing icterus, intermittent fever and digestive disturbances and died six months after surgical therapy was instituted. Autopsy showed that the stoma of the previous anastomosis was permeable but that the intrahepatic biliary ducts were filled with pus. It may be noted as indicating the slow progress of the disease that the tumor was not appreciably larger at this time than at first inspection and preserved the same general contour. In Weber and Michels' case, celiotomy on two occasions within two months failed to reveal the cause for jaundice which had persisted for three months. At the second operation a hole 3 cm. deep was bored into the liver by an electrocautery, and a drainage tube was placed within it. Jaundice gradually disappeared, and there was a gain in weight, although occasional vomiting occurred. A month and a half later irregular fever, edema and slight purpura of the legs developed, which terminated fatally within two weeks. Autopsy showed that biliary obstruction was due to an infiltrating tumor confined to the confluence of the bile ducts. The fistulous opening produced at the second operation communicated with one of the intrahepatic biliary ducts. Tuberculous foci were widely disturbed in the lungs, the spleen, the peritoneum, the omentum and the lymph nodes at the hilus of the liver. In Brenner's case a cherry-sized tumor was palpated near the duodenum. Seventy-three gallstones were removed from the gallbladder, a portion of which was excised, and a drain was inserted. At the second celiotomy, one and a half months later, an abscess lying between the gallbladder and the liver was evacuated, and a cholecystoenterostomy was established. At the third celiotomy the cholecystoenterostomy was separated, and the dilated bile duct was implanted into the previous opening in the intestine. Death followed three months after the first operation, and autopsy revealed fibrinous peritonitis and metastases in the liver and regional lymph nodes.

These cases illustrate a number of interesting facts. Although no cure was effected by surgical therapy, the condition is not entirely hopeless. Any operation designed for drainage of the distended biliary tract by utilization of the extrahepatic biliary ducts below the highest point of the neoplasm would of course be ineffective in obviating bile stasis. The higher the neoplasm extends toward the liver, the more difficult surgical drainage becomes. In this connection, the procedures of anastomosing the jejunum to the incised liver as in Lameris' case and of puncturing the liver and draining the intrahepatic biliary ducts as in Weber and Michels' case are no doubt justifiable on occasion. Of the 6 patients who survived four months or longer after operation, death was apparently due to ascending biliary tract infection in 5; no information on this feature was available in Quénu and Gasne's case, for no autopsy was performed. The case of Lameris and that of Mondor also serve to emphasize the slow growth of these neoplasms, for in the latter no change

in size was detected after an interval of six months, and in the former the neoplasm increased only from the size of a walnut to that of a hen's egg during nine months. Metastases were noted in Brenner's case five months after the onset and (incidentally) in Borelius' case six months after onset.

Generally speaking, then, symptoms appear early, the neoplasm is slow growing and metastases occur late. The gravest concern is the high immediate postoperative mortality (66.6 per cent). Of significance is the fact that these patients were ill for about four months on the average before operation as contrasted with two months for those patients who survived for three months or longer after operation. Early

TABLE 3.—*Results in Cases of Carcinoma of the Common Bile Duct in Which Operation Was Performed*

Year	Author	Operation	Result
1896	Griffon and Dartiques	Cholecystostomy	Patient died 7 days after operation
1902	Uliszewski, case 1	Resection of gallbladder, cystic duct and common bile duct; drainage of hepatic duct	Patient died 3 days after operation
1908	Borelius, case 2	Exploratory operation	Patient died 2 days after operation
1909	Morian, case 4	Resection; cholecystoduodenostomy	Patient living and well 10 months after operation
1917	Petrén, case 20	Cholecystoenterostomy	Patient died 2 days after operation; hemorrhage
	Case 22	Cholecystectomy; drainage of hepatic duct	Patient died several hours after operation
1930	Shapiro and Lifvendahl, case 10	Cholecystostomy	Patient died 7 days after operation; hemorrhage
1935	Demel	Resection; subserous cholecystectomy; hepaticoduodenostomy; anastomosis of cut ends of ducts	Patient died 7 months after operation

diagnosis and early operation while the patient's condition is not yet critical yield vastly more satisfactory results, according to these figures. Although the surgeon has a limited field in which to work, in a number of the cases cited resection of the primary neoplasm followed by reestablishment of biliary flow by implantation of the hepatic duct into the gastrointestinal tract was satisfactorily accomplished. There was an immediate surgical mortality of 66.6 per cent. The total survival period from the onset to death in the surgically treated group averaged seven and sixteen hundredths months, as compared with four and six-tenths months for the patients treated medically only.

Carcinoma of the Common Bile Duct.—Thirteen patients were treated medically only and lived from one to eleven months after onset, averaging four and four-tenths months.

Surgical therapy was instituted in 8 cases, and the operative procedures and results are indicated in table 3. The primary neoplasm was

detected by external palpation of the ducts at celiotomy in 4 cases and by attempting to pass a sound into the duct, which was obstructed in 1 case; in 3 cases the tumor was missed. The palpable growths varied from the size of a pea to that of a walnut; in 2 cases, metastatic deposits were present in the regional lymph nodes. The gallbladder was distended in 6 cases, containing clear, colorless fluid in 4 and tarlike fluid and stones in 1 each; no mention of this viscus was made in 2 cases.

No reference was made in any case to the general state of the patient during the postoperative period. Six patients died during the first seven postoperative days. The 2 patients who survived the immediate effects of operation are to be cited. At celiotomy in Demel's case, a pea-sized polypoid tumor in the proximal portion of the common bile duct was excised, together with the cystic duct and the gallbladder. A rubber tube was inserted through the papilla of Vater into the hepatic ducts, and severed ducts were anastomosed. Five weeks later the rubber tube was spontaneously evacuated. The patient died seven months after operation, but no autopsy was performed. In Morian's case, a tumor the size of a hazelnut in the distal part of the common bile duct was excised, and the gallbladder was anastomosed to the duodenum. The patient was still alive ten months after operation, although no "interim notes" were available. The duration of the disease from onset to death for the surgically treated patients averaged about two and two-tenths months in contrast to an average of four and four-tenths months for the patients treated medically only.

SUMMARY AND CONCLUSIONS

A clinical and pathologic study of carcinoma of the extrahepatic bile ducts is presented, based on 6 new cases and 98 cases satisfactorily reported in the literature; references to 211 additional cases reported under this title in the literature are listed.

One case was found in a series of 3,528 autopsies (0.028 per cent) and 5 cases in a series of 22,152 autopsies (0.022 per cent).

The average age was 59.3 years. Seventy-three patients were men, and 31 were women. In 3 cases, carcinoma of the hepatic duct occurred in comparatively young persons, aged respectively 29, 31 and 32 years.

The onset was acute in 88.5 per cent of cases and gradual in 11.5 per cent. The principal symptoms and signs, irrespective of the mode of onset, were jaundice, loss of weight and strength, pain, pruritus, anorexia, fever, vomiting, diarrhea, constipation and nausea. Other, less common symptoms were abdominal distention, chills, a sense of weight or pressure in the abdomen, flatulency and belching. Jaundice occurred in every case and pain in 52.9 per cent, and the two were associated at the onset in about 10 per cent. With carcinoma of the hepatic and common bile ducts, jaundice occurred equally early and late in the con-

dition, but with carcinoma of the confluence of the three ducts a majority of patients exhibited jaundice later, in about the proportion of 5 to 3. Fever, sometimes with chills, occurred in 26 per cent of cases, usually late. In no instance was a mass in the region of the primary tumor clinically palpable. The liver was palpably enlarged in 68 per cent of cases and the gallbladder in 26 per cent. A varying grade of anemia was the rule in the few cases in which the blood was examined. The gastric contents were examined in 9 cases and showed absence of free hydrochloric acid in 6 instances and the presence of lactic acid in 4, bile in 2 and blood in 1. The stools were usually clay colored or colorless; they were occasionally fetid, and they contained an excess of fat in 7 cases; blood was detected in 9 of 15 stools tested.

A correct provisional preoperative clinical diagnosis was made in about 20 per cent of cases. A correct surgical diagnosis was made in 36 per cent of cases in which celiotomy was done. Roentgen studies were of no direct value as an aid in clinical diagnosis.

The primary neoplasm in the group of cases of carcinoma of the hepatic duct (35 cases) formed a local tumor in 75 per cent. The growth averaged 2 cm. in diameter and consisted usually of an annular, constricting, grayish white lesion, with ulceration in 4 cases. A diffuse growth was present in 25 per cent of cases, with additional characteristics of widespread involvement and a tendency to extend into the liver in a wedge-shaped manner. Extension or metastases occurred in 48.5 per cent of cases, to the liver, lymph nodes, pancreas, gastrohepatic ligament and mediastinum. All the neoplasms were adenocarcinomas. In 1 case in this group there were multiple white infarcts of the liver, an extremely rare finding in the presence of biliary stasis in human beings. Variability in the size of the gallbladder in the group with carcinoma of the hepatic duct is to be contrasted with the findings in cases of carcinomatous obstruction at or below the terminal orifice of the cystic duct. Under the latter circumstances cholecystic distention regularly takes place unless the gallbladder has been previously thickened and atrophied by disease.

The neoplasms in the group with carcinoma of the confluence of the extrahepatic bile ducts (48 cases) formed a local tumor growth in 56.3 per cent of cases and a diffuse growth in 43.7 per cent. The local tumors were usually of the size of a hazelnut and formed either a single elevated projection above the mucous surface or an annular, constricting, gray, firm cartilaginous lesion. The diffuse type of neoplastic involvement was more extensive and appeared gray or white and fibrous or cartilaginous. Extension or metastases occurred in 45.8 per cent of cases, to the liver, lymph nodes, gallbladder, lung, peritoneum, pancreas, kidney and spleen. All the neoplasms were glandular carcinomas.

The neoplasms in the group with carcinoma of the common bile duct (21 cases) formed a local tumor growth in 57 per cent of cases and a diffuse growth in 43 per cent. The local tumors varied in size from a few millimeters to the size of a walnut and were soft, gray or white, with a granular or papillary surface. The diffuse growths were firm, stenosing, granular and vegetating on the surface. Extension or metastases occurred in 52.3 per cent of cases, to the liver, lymph nodes, lungs and gallbladder. The neoplasms were glandular carcinomas, with 1 exception, which was a squamous cell carcinoma.

The well known law for localization of cancer of the bile ducts at points of narrowing of the stream bed seems valid. Gallstones occurred in 20.2 per cent of cases.

An indubitably proved case of primary carcinoma of the cystic duct has not been found reported in the literature.

Surgical therapy was instituted in 50 cases. There was an ultimate mortality rate of 98 per cent, the fate of 1 patient remaining unrecorded. Included in this mortality rate figure is another case (Pallin) in which there was an eleven month postoperative survival period and in which no cancer could be demonstrated at autopsy. The immediate postoperative mortality rate was 68 per cent. Three patients with carcinoma of the hepatic duct survived for an average of three and six-tenths months after operation, and another was still living at the end of four and five-tenths months. The average total survival period for the 21 patients treated surgically in this group was six and forty-eight hundredths months as compared with eight and eight-tenths months for 12 of the 14 patients treated medically only. Seven patients with carcinoma of the confluence of the extrahepatic bile ducts survived for an average of eleven and five-tenths months after operation. The average total survival period for the 21 patients treated surgically in this group was seven and sixteen hundredths months, as compared with four and six-tenths months for 26 of the 27 patients treated medically only. One patient with carcinoma of the common bile duct survived for seven months after operation, and another was still living at the end of ten months. The average total survival period for 8 patients treated surgically in this group was about two and two-tenths months, as compared with four and four-tenths months for the 13 treated medically only. Early diagnosis is essential, and laparotomy performed early, when the patient's general condition is not yet critical, gives appreciably better results, according to the figures derived from this study. The effectiveness of this element is illustrated by the fact that the patients with carcinoma of the confluence of the extrahepatic bile ducts who succumbed to the immediate effects of operation were ill for an average of four months before operation, as contrasted with about two months for those patients who survived for three months or longer after operation.

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METAPLASIA IN THE BREAST

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A comprehensive examination of the literature has revealed no reference to the presence of pavement epithelium of primary origin in the mammary gland. Numerous reports, however, of metaplasia and its associated changes prove its frequency and include descriptions of its occurrence in several organs of the body, among which are the nose, frontal sinus, middle ear, lungs, esophagus, stomach, gallbladder, pancreatic duct, renal pelvis, bladder, urethra, uterus and ovary. It is doubtful that metaplasia has actually been found in many of the reported cases, owing to the possibility of epithelium growing over from adjacent lesions of the skin or of the mucous membrane. Naturally, all fistulas warrant suspicion. The greatest offenders in the production of metaplasia have been reported as chronic inflammatory processes.

Consideration of a subject so complex as metaplasia and its associated processes demands brief mention of the striking figures in a literature which is muddled with a confusing terminology to which few authors have neglected to add.

Metaplastic processes in which there are simple changes in the configuration of the cells are commonly known under the nomenclature of von Hansemann and Borst [1] as histologic accommodation or variation. Other appellations of the same processes are Lubarsch's pseudometaplasia, Orth's [1] allomorphia and Ribbert's [1] retrogression.

Lubarsch [2] admirably described two processes. One is physiologic loss of differentiation through imperfect cell division. The other is pathologic loss of differentiation, which leads to destruction of cells by degeneration and atrophy in fully differentiated tissues. He termed these processes dedifferentiation. These changes are similar to those of Beneke's cataplasia and von Hansemann's anaplasia.

The term metaplasia, by which is meant the substitution of a specific cell or tissue for another differentiated cell or tissue, has been rejected

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1. Cited by Buchmann.[4]

2. Lubarsch, O.: The Question of Metaplasia and Its Significance in Tumors, Arb. a. d. path. anat. Abt. d. k. hyg. Inst. zu Posen. R. Virchow zur Feier, 1901, pp. 205-232; Metaplasia, Centralbl. f. allg. Path. u. path. Anat. **17**:884-885, 1906; The Question of Metaplasia, Verhandl. d. deutsch. path. Gesellsch. **10**:198-208, 1906-1907.

by most authors in the strict sense of the word, as it is doubtful that such a direct change ever takes place. Transitional stages in the production of metaplastic processes in an indirect manner have been stressed by Ribbert and Schridde.[1] This view has been substantiated by Lubarsch,[2] Orth,[1] Gruber [3] and Buchmann [4] and is the more plausible course of development.

The researches of Stoeckenius,[5] Wenslaw [6] and Harms [7] show rather conclusively that all sorts of variations and malformations may arise from germinal tissue, and that under certain conditions fully developed epithelium may regain its embryonal aspect.

The striking relation between metaplasia and cancer formation, in that mechanical injuries and chronic inflammations are given as causes for both, has been noted by Buchmann,[4] who went further and stated that in many cases cancer is brought about by metaplasia of epithelium. Gruber [3] expressed the opinion that tumors with epithelium foreign to the site are suggestive of metaplasia but that it is more probable that they are due to malformations of embryonic tissue. Lubarsch [2] expressed the belief that metaplasia in cancer is rare.

In summarizing and presenting my own views it seems best to consider the possible mechanisms by which metaplasia and its associated processes may be brought about.

(*a*) In consideration of the derivation of metaplastic processes from a germinal cell or tissue, it must be understood that certain cells of the original germinal stock from which the specialized cell or tissue is derived may remain undifferentiated, though they are carried along with the differentiated cells in their development. Their presence in the specialized tissue is explained by this peculiar migration or displacement. The development of these immature cells with respect to the differentiated cells may proceed in a different direction.

(*b*) It can easily be seen that in the growth of cells or a tissue toward a certain specialization, there is a possibility that some cells may be retarded in their differentiation and may remain so, as do the completely undifferentiated cells in the specialized tissue. These cells, likewise, may develop along lines foreign to the site, thus presenting an appearance different from that of the tissue under consideration.

(*c*) The transformation of one specialized cell or tissue into another specialized cell or tissue of a different type is doubtful and rarely, if

3. Gruber, G. B.: Metaplasia, München. med. Wchnschr. **61**:609-612, 1914.

4. Buchmann, E.: The Present Status of the Metaplasia Question, Cor.-Bl. f. schweiz. Aerzte **41**:270-283, 1911.

5. Stoeckenius, W.: Data on Metaplasia, Klin. Wchnschr. **4**:1029-1033, 1925.

6. Wenslaw, A.: Experimental Investigation on Metaplasia of the Pulmonary Epithelium, Compt. rend. Soc. de biol. **106**:363-367, 1931.

7. Harms, W.: Experimental Metaplasia in Rana Fusca Rös, Zool. Anz. **42**:49-55, 1913.

ever, occurs in a direct manner, although this possibility must be considered.

In groups *b* and *c* the question of retrogression and variation arises. The partially differentiated cell or tissue as well as the completely differentiated cell or tissue may undergo transitional regressive changes, either in part or to the point of appearing as a completely undifferentiated cell. This process may be accounted for by the formation and nutrition of cells as set forth by Virchow.[8] The further development, then, along different lines in a direct manner may take place, although the whole process must be considered indirect, as transitional changes are necessary for the transformation of one given cell or tissue into another given cell or tissue which is specialized.

The later development along lines different from those followed by the specialized tissue is augmented in many instances by certain external forces, such as chronic irritation, mechanical stimuli and tumors, and by internal factors which have yet to be determined.

The mammary glands arise from a knoblike thickening of the ectoblast, occurring during the second month of fetal life. This thickening sinks into the underlying mesoblastic tissue, which undergoes proliferation and condensation and forms an investment for the growing epithelial mass. From this envelop the fibrous and muscular tissue of the areola and the nipple are derived, while the underlying mesoblast produces the connective tissue stroma. Solid epithelial sprouts grow out from the sides of the epidermal ingrowth and are the first anlages of the true mammary gland, later becoming the excretory ducts. Subsequently, the central part of the ectoblastic plug undergoes degeneration and destruction, and what at first was an elevation becomes a depression. From the middle of the depressed area there appears, just prior to birth, an elevation which later becomes the nipple. Meanwhile, the epithelial ductal outgrowths penetrate the surrounding condensed stroma, increase in length, subdivide and acquire a lumen at their distal ends, due to desquamation of the central plug, thus giving rise to the system of ducts and lobules of immature gland tissue. With further development the surrounding stroma is broken up into the interlobular septunis and fibrous framework. At birth the gland is represented by the lactiferous ducts with their ampullae, the smaller ducts and the immature alveoli. Temporary activity may occur in either sex a few days after birth, giving rise to the so-called witch's milk. The glands remain more or less stationary during childhood.

A brief review of the physiology of the breast and of the abnormalities associated with faulty cyclic processes, described by Oliver and

8. Virchow, R.: About Metaplasia, Virchows Arch. f. path. Anat. **97**:410-430, 1884.

Major [9] as cyclomastopathy, is presented with the hope of showing the major offending mechanism in the cases to be reported.

Before the changes associated with puberty the breast consists chiefly of connective tissue in which there are a few ducts without definite lobular structure. The parenchyma is divided, however, into systems of ducts varying in number from ten to twenty, the main duct of each

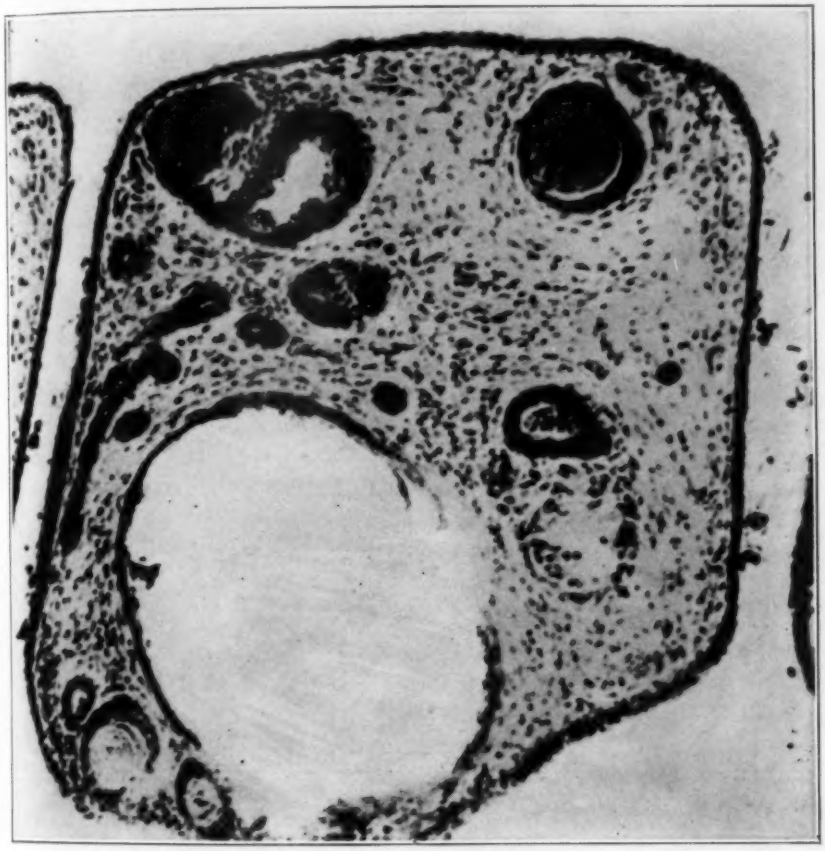

Fig. 1 (case 1).—Photomicrograph showing variations in epithelial structure in a loose connective tissue stroma. This projection of tissue was found extending into a cyst or a dilated duct.

emerging individually at the nipple. The lobes are rather indistinctly separated by bands of fibrous tissue blending anteriorly with the skin and posteriorly with the chest wall.

9. Oliver, R. L., and Major, R. C.: Cyclomastopathy: A Physio-Pathological Conception of Some Benign Breast Tumors, with an Analysis of Four Hundred Cases, Am. J. Cancer **21**:1-85, 1934.

The changes at puberty occur as a result of hyperplasia of the periductal and interlobular connective tissue and of the ductal epithelium, which forms new branches. These changes are frequently accompanied with excessive proliferation of one or more of these elements, and local or diffuse hyperplasia results.

The hypertrophy of the breast during lactation consists of hyperplasia of the ductal and acinar epithelium and transient increase in the

Fig. 2 (case 1).—Photomicrograph showing a projection into a cystic cavity. The epithelium is definitely squamous, and some keratinization is seen. Pearly bodies are prominent.

intralobular connective tissue. Excessive growth of the parenchyma occurs in some instances but usually disappears with the ensuing involutionary process. Abnormal involution combined with exaggerations of proliferation of the periductal and periacinar connective tissue are as important in the formation of the cyclomastopathic processes as are the changes occurring at puberty.

There is some epithelial hyperplasia in the premenstrual phase of the menstrual cycle and hyperplasia of the connective tissue in the post-

menstrual phase. The variety of combinations of epithelial and connective tissue elements presents evidence that there is some hyperplasia of both throughout different parts of the cycle, leading one to assume that the same lobule or lobules which respond to stimuli occurring in this cycle may involute with more than normal vigor, or vice versa. It is clear that no hypertrophied nodule is left without being acted on and modified by additional stimuli.

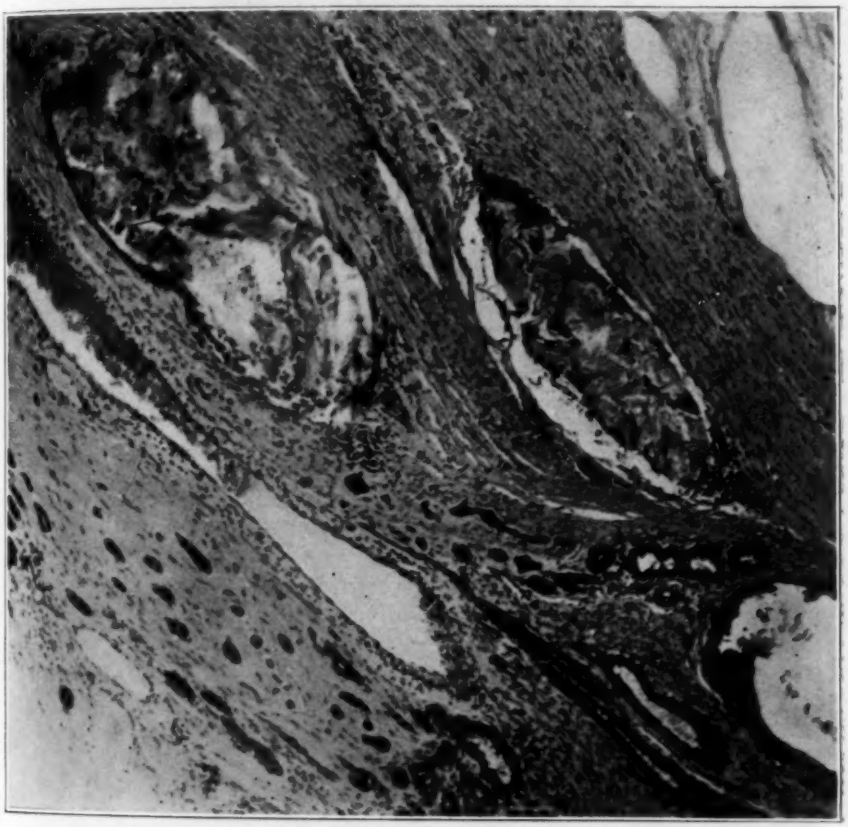

Fig. 3 (case 2).—Photomicrograph showing the compressed capsule of the encapsulated tumor.

It is obvious that the cyclic processes may show local nodules or diffuse involvement of one or both breasts. These processes may present excessive proliferation of epithelial or connective tissue, or both, in response to growth stimuli. Abnormal processes may be present as a result of faulty involution. These proliferations or involutions, separately

or together, are aptly called cyclomastopathies. It is in these cyclomastopathic processes that the finding of epithelial metaplastic elements is reported.

REPORT OF CASES

CASE 1.—A white married woman aged 50 complained of a tumor of the right breast of eight months' duration. On examination there was a large, fungating

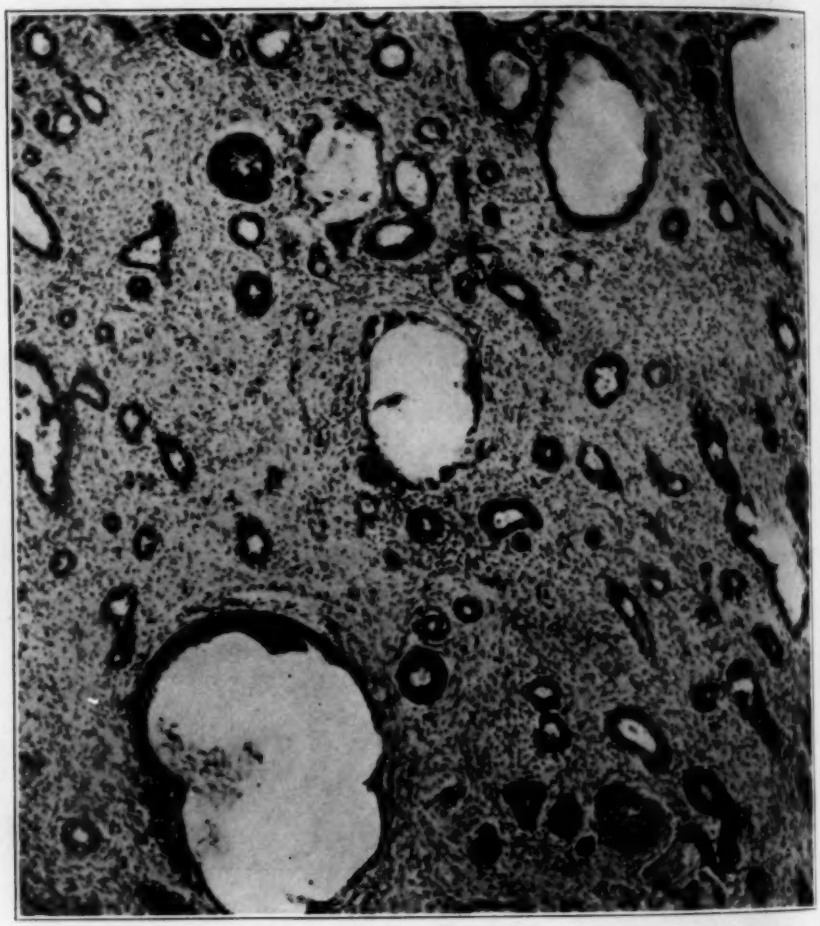

Fig. 4 (case 2).—Photomicrograph showing ducts and acini lined with a cuboidal or modified pavement type of cell.

circumscribed mass in the lower part of the breast. It was clinically malignant. The breast was amputated. The patient was followed for five years and was well at the end of that time.

The mass was encapsulated. Portions of the capsule contained some lobules of compressed tissue and fat. The mass was composed of a very dense stroma con-

taining many distorted structures lined by epithelium varying from squamous to columnar. The dense stroma appeared to be chiefly of interlobular origin, as few ducts or alveoli were arranged in groups. There was also intralobular hyperplasia, in that the intralobular markings were very indistinct, and the cells in general were of the same type. The ducts, where they were enlarged, were considerably

Fig. 5 (case 3).—Photomicrograph showing some acini filled with a transitional type of epithelium. Other dilated ducts are lined with columnar epithelium.

compressed. Some areas of hyalinization could be seen. The epithelial structures varied in size, and some cystic areas were noted. One of the larger cysts was lined with epithelium of pavement type, with definite keratosis and hornification. Pearly bodies were distinctly seen in small groups just beneath the wall of this

cyst. Transitions were noted between this type and the glandular type in the same section.

CASE 2.—A single white girl aged 16 had a slowly growing tumor of seven years' duration in the left breast. It was a lobular, hard, encapsulated, movable mass the size of one-half the breast and was clinically benign. It was excised. The ultimate result is unknown.

The mass was encapsulated and composed of a dense stroma containing many parenchymal structures. Some of the epithelial elements were dilated, and many huge papillae of hyperplastic connective tissue projected into the dilatations. The epithelial cells varied from glandular cells to modified pavement cells, some of which showed keratosis. There were no areas, however, which showed the extensive keratinization observed in case 1.

CASE 3.—A white married woman aged 46 complained of a tumor of the right breast, with pain, of six months' duration. There was a history of rapid growth for the last two months. There was a firm, nodular, movable mass with areas of softening in the upper part of the breast, and it was clinically malignant. The complete operation for cancer was done, including dissection of the axilla. This patient remained well nine years after operation.

The mass was encapsulated. The tumor was composed of a rather dense stroma with many dilated epithelial structures of varying appearance. Some of the lining epithelium was of an orderly arrangement and composed of two definite layers, while other parts showed some piling up of epithelium with growth into the dilated cavities in the form of small papillae. This hyperplastic growth in some instances had an adenomatous appearance. There were a few definite cystic areas, as well as areas showing hyalinization. One of the larger cysts, in particular, was lined partly by pavement epithelium with hornification, which gradually merged into types of cuboidal to columnar arrangement.

COMMENT AND CONCLUSION

These cases are of importance in that the discovery of a pavement type of epithelium in the mammary gland is described in detail for the first time. It must be noted that this type of epithelium was deeply embedded in growths of cyclomastopathic origin and in no way could have been the result of the growing over of surface epithelium, which must be ruled out in all cases of suspected metaplastic processes. The presence of pavement epithelium in such a growth bears out the contention that mechanical stimuli may aid in inaugurating metaplastic processes. Whether embryonal displacement, simple retrogression into a kind of cell similar to the one from which it was derived or direct metaplasia is responsible for the change is a purely theoretic question. The fact remains that the change has taken place, and it is associated with changes similar to metaplasia and must be considered under this heading. The variation from the glandular to the pavement type of cell indicates strongly that the process is an indirect one, transitional changes being necessary for the transformation, as against the direct method, in which one specialized cell or tissue is changed into another specific cell or tissue without intermediate stages. No such abrupt change was seen in any of the sections.

SERUM PROTEINS AND WOUND HEALING

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Although many studies of serum proteins in the human being in the normal state and in various pathologic conditions have been published,[1] apparently no studies of serum protein concentration in relation to wound healing have been reported.

We have studied the concentrations of total protein, albumin and globulin, the albumin-globulin ratio and the calculated protein oncotic pressure of the serum of 58 patients in the postoperative state whose wounds were carefully observed. In the cases of 17 who had hernioplasties with clean wounds (table 1) the determinations were done from one to ten days after operation (average four days). In the cases of 23 who had abdominal operations with clean wounds (table 2) the determinations were done from one to twenty-two days postoperatively (average eight days). In the cases of 16 who had abdominal wounds complicated by deep infections extending below the fascia (table 3) the determinations were done from one to twenty days postoperatively (average eleven days). In the cases of 8 who had clean wounds which disrupted during convalescence (table 4) the determinations were done from five to ten days postoperatively (average eight days).

All wounds were sutured with catgut in the deeper layers and with black silk in the skin. In the hernioplasty wounds the internal oblique muscle and the conjoined tendon (Bassini) or the internal oblique muscle, the conjoined tendon and the external oblique aponeurosis (Ferguson-Andrews) were sutured to the inguinal ligament with interrupted no. 2 chromic catgut. In the abdominal wounds the peritoneum was closed with continuous no. 2 plain catgut and the fascia with continuous no. 2 chromic catgut. In all the cases the black silk in the skin was a continuous suture.

The values for total serum protein were determined by aeration and titration after micro-Kjeldahl digestion.[2] The values for albumin were determined after precipitation of globulin with sodium sulfate [3]

From the Surgical Service of the Crown Heights Hospital.

1. Bennhold, H.; Kylin, E., and Rusznyák, S.: Die Eiweisskörper des Blutplasmas, Dresden, Theodor Steinkopff, 1938.

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TABLE 1.—*Clean Hernioplasty Wounds*

Age of Patient	Operation	Days Between Operation and Determination	Protein, Gm. per 100 Cc. Serum	Albumin, Gm. per 100 Cc. Serum	Globulin, Gm. per 100 Cc. Serum	Albumin-Globulin Ratio	Protein Oncotic Pressure, Cm. H_2O
52	Inguinal hernioplasty	2	8.40	5.53	2.87	1.92	41
56	Bilateral inguinal hernioplasty	1	8.30	5.33	2.97	1.80	41
43	Bilateral inguinal hernioplasty	3	6.85	4.69	2.16	2.17	30
41	Inguinal hernioplasty	10	7.13	3.90	3.23	1.25	27
65	Inguinal hernioplasty	2	6.75	4.42	2.33	1.90	28
33	Bilateral inguinal hernioplasty	2	6.88	4.65	2.23	2.08	30
17	Inguinal hernioplasty	4	7.25	4.89	2.36	2.07	33
47	Galli hernioplasty for recurrent inguinal hernia	5	7.57	4.77	2.80	1.70	32
24	Galli hernioplasty for recurrent inguinal hernia	2	7.68	4.89	3.29	1.33	31
52	Inguinal hernioplasty	2	7.75	4.76	2.99	1.59	32
42	Bilateral inguinal hernia	2	5.74	4.38	1.36	3.22	25
54	Inguinal strangulated hernia	8	5.87	3.64	2.23	1.63	22
46	Torex operation for undescended testicle; inguinal hernioplasty	2	5.88	3.46	2.42	1.43	21
43	Inguinal hernioplasty	3	5.95	4.21	1.74	2.42	25
21	Inguinal hernioplasty	9	6.75	3.46	3.29	1.05	23
48	Inguinal hernioplasty	1	6.15	4.58	1.57	2.92	27
41	Inguinal hernioplasty	8	6.09	3.84	2.25	1.70	23

TABLE 2.—*Clean Abdominal Wounds*

Age of Patient	Diagnosis	Operation	Days Between Operation and Determination	Protein, Gm. per 100 Cc. Serum	Albumin, Gm. per 100 Cc. Serum	Globulin, Gm. per 100 Cc. Serum	Albumin-Globulin Ratio	Protein Oncotic Pressure, Cm. H_2O
55	Cancer of stomach	Subtotal gastrectomy (Polya)	8	7.88	4.62	3.26	1.42	34
36	Recurrent cholecystitis and cholelithiasis with common duct obstruction	Laparotomy; cholecystectomy; T-tube drainage of common bile duct	14	6.38	4.61	1.77	2.60	28
42	Acute appendicitis	Appendectomy	10	6.74	4.58	2.16	2.12	27
32	Acute appendicitis	Appendectomy	9	6.05	3.85	2.20	1.75	20
30	Chronic appendicitis	Appendectomy	7	6.20	3.90	2.30	1.69	25
32	Acute appendicitis (gangrenous); intestinal obstruction	Appendectomy	19	6.69	4.12	2.57	1.60	26
32	Neuroma of appendix; early regional ileitis	Appendectomy; removal of biopsy specimen	12	6.01	3.69	2.32	1.59	23
53	Fibroid uterus	Hysterectomy (supracervical); appendectomy	5	6.17	4.05	2.12	1.90	25
40	Chronic cholelithiasis	Cholecysteetomy; appendectomy	11	7.51	4.04	3.47	1.16	29
22	Acute gangrenous appendicitis	Appendectomy	10	6.53	4.33	2.20	1.97	27
18	Ruptured ovarian cyst	Appendectomy; excision of cyst of ovary	9	6.50	4.74	1.85	2.56	30
29	Chronic appendicitis	Appendectomy	11	6.72	4.19	2.53	1.65	27
31	Chronic appendicitis; retroverted uterus	Appendectomy; suspension of uterus; plication of cecum	7	7.06	3.76	3.30	1.14	26
53	Chronic cholecystitis and cholelithiasis	Cholecysteetomy; appendectomy	1	7.40	4.02	3.38	1.19	30
39	Chronic appendicitis	Appendectomy	7	5.46	3.52	1.94	1.81	21
46	Scleroderma; fibroid uterus; chronic cholelithiasis	Supracervical hysterectomy; right salpingo-oophorectomy; appendectomy; perineorrhaphy; cholecystectomy	22	5.75	2.82	2.93	0.96	15
31	Cholelithiasis	Cholecystectomy	3	7.90	5.24	2.66	1.97	33
31	Duodenal ulcer	Subtotal gastrectomy (Polya)	1	7.82	5.13	2.69	1.90	36
46	Chronic cholecystitis; fibroid uterus	Cholecysteetomy; supracervical hysterectomy; left salpingo-oophorectomy	6	6.72	4.12	2.60	1.58	27
38	Chronic cholelithiasis; common duct obstruction	Cholecystectomy; choledochostomy; appendectomy	5	6.60	3.18	3.42	0.93	22
50	Bleeding duodenal ulcer	Subtotal gastrectomy (Polya)	10	7.60	3.54	4.06	0.87	26
49	Gastric ulcer	Subtotal gastrectomy (Polya)	1	5.95	3.84	2.11	1.82	23
40	Fibroid uterus; chronic pelvic inflammatory disease	Supracervical hysterectomy; bilateral salpingo-oophorectomy; appendectomy perineorrhaphy	2	5.64	4.56	1.08	4.22	28

(Na_2SO_4). Oncotic pressure was estimated from empiric curves based on the observations of Wies and Peters.[4]

The results are summarized in table 5.

COMMENT

Harvey and Howes [5] noted an improvement in the rate of healing of gastric wounds in rats on a high protein diet. Thompson, Ravdin and Frank [6] reported that after abdominal incision the wounds of 8 of 11 dogs previously fed a restricted diet and subjected to repeated plasmapheresis disrupted or failed to heal. Although they gave no figures for serum protein, they stated, on the basis of previous studies, that the dogs had definite hypoproteinemia. They suggested that this was a factor in the mechanism of wound disruption. As a result of failure to produce disruption in 3 similarly prepared dogs which subsequently received lyophilized serum intravenously to raise the serum protein content, they suggested [7] that "retardation in healing of wounds associated with hypoproteinemia in dogs may be averted by restoration of the serum protein to normal levels immediately after operation."

However, the absence of data on the actual concentration of serum protein and its fractions in their experimental animals makes it difficult to evaluate their results or to attempt to apply them to human beings. It is also worth noting that their observations were made on dogs suffering not merely from hypoproteinemia. There is, indeed, little evidence that hypoproteinemia was the only metabolic disorder in their animals, maintained as they were on a restricted diet and subjected to repeated plasmapheresis.

In our studies the values for the total proteins and fractions in the cases of patients with clean abdominal and hernial wounds are similar to the values reported in the literature for normal human beings.[1] On the other hand, the average values for total protein, albumin and oncotic pressure in the cases of patients with deep infection and disruption were slightly but definitely lower than normal. The value for globulin remained unchanged. Whatever hypoproteinemia was present was therefore actually hypoalbuminemia (table 5).

4. Wies, C. H., and Peters, J.: Osmotic Pressure of Proteins in Whole Serum, J. Clin. Investigation **16**:93, 1937.

5. Harvey, S. C., and Howes, E. L.: Effect of High Protein Diet on the Velocity of Growth of Fibroblasts in the Healing Wound, Ann. Surg. **91**:641, 1930.

6. Thompson, W. D.; Ravdin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption, Arch. Surg. **36**:500 (March) 1938.

7. Thompson, W. D.; Ravdin, I. S.; Rhoads, J. E., and Frank, I. L.: Use of Lyophile Plasma in Correction of Hypoproteinemia and Prevention of Wound Disruption, Arch. Surg. **36**:509 (March) 1938.

TABLE 3.—*Deep Infection in Abdominal Wounds*

Age of Patient	Diagnosis	Operation	Days Between Operation and Determination	Protein, Gm. per 100 Cc. Serum	Albumin, Gm. per 100 Cc. Serum	Globulin, Gm. per 100 Cc. Serum	Albumin-Globulin Ratio	Protein Oncotic Pressure, Cm. H_2O	Comment
66	Acute gangrenous appendicitis with perforation; paralytic ileus; terminal hepatitis	Appendectomy; jejunostomy	9	5.22	3.44	1.78	1.93	19	Deep infection; fascial slough on 7th day; patient died with terminal hepatitis on 32d day
72	Acute gangrenous appendicitis with perforation and abscess	Appendectomy	9	6.05	3.36	2.69	1.25	21	Acute heart failure on the left on 2d day; acute parotitis on 8th day; foul bloody collection evacuated on 8th day, with extensive fascial slough; pneumonia on 33d day; patient died on 36th day
31	Chronic cholecystitis	Cholecystectomy; appendectomy	18	6.51	3.37	3.14	1.07	23	Large collection evacuated from incision on 9th day; wound opened on 10th day, exposing extensive slough of all layers; healed uneventfully after packing
55	Postoperative abdominal fistula with subhepatic abscess	Drainage of subhepatic abscess; choledochostomy	12	5.22	2.86	2.36	1.21	17	Deep infection which drained pus around through and through sutures and continued to drain for several weeks
63	Acute gangrenous cholecystitis and cholelithiasis	Cholecystectomy	9	5.94	3.20	2 74	1.17	20	Deep collection evacuated on 8th day; healed uneventfully after packing
42	Intestinal obstruction due to postoperative adhesions	Separation of adhesions; Witzel enterostomy	3	5.69	3.37	2.32	1.45	20	Extensive gangrene of wound edges on 2d day; patient given gas gangrene antitoxin; wound healed after treatment with peroxide irrigations and packing

26	Acute appendicitis (gangrenous)	Appendectomy	7	5.55	3.64	1.91	1.90	21	Deep infection with slough of fascia evacuated on 5th day; wound healed uneventfully after packing
24	Acute gangrenous appendicitis	Appendectomy	8	5.75	3.04	2.71	1.12	19	Marked distention; foul collection in wound evacuated on 8th day; healed uneventfully after packing; pneumonia with pleural effusion on 16th day; patient discharged on 48th day
62	Chronic cholelithiasis, common duct stone; nephroptosis lipomas	Cholecystectomy; choledochostomy; nephropexy; appendectomy; excision of lipomas	20	5.61	3.44	2.17	1.57	21	Deep infections in all 3 wounds; healed uneventfully after packing
58	Lymphosarcoma of rectum	One stage abdominoperineal resection of rectum	10	4.79	2.39	2.40	0.99	14	Foul collection with fecal contamination evacuated from wound on 6th day; edema of abdominal wall, legs and scrotum on 6th day; evisceration after coughing spell on 11th day; suppurative epididymitis on 15th day; stormy course, but wounds healed after packing and patient was discharged on the 30th day
30	Gangrenous Meckel's diverticulum	Appendectomy; resection of Meckel's diverticulum	22	5.89	4.35	1.54	2.82	26	Deep purulent collection evacuated on 4th day; wound healed uneventfully after packing
57	Acute gangrenous cholecystitis	Cholecystectomy; appendectomy	11	6.76	4.32	2.44	1.77	28	Pneumonia on 6th day; deep collection evacuated on 6th day; wound healed uneventfully after packing; patient discharged on 46th day
23	Acute appendicitis	Appendectomy	8	7.03	4.57	2.46	1.86	30	Foul collection of brownish fluid evacuated on the 7th day; wound healed uneventfully after packing

TABLE 4.—*Wound Disruption*

Age of Patient	Diagnosis	Operation	Days Between Operation and Determination	Days Between Operation and Disruption	Protein, Gm. per 100 Cc. Serum	Albumin, Gm. per 100 Cc. Serum	Globulin, Gm. per 100 Cc. Serum	Albumin-Globulin Ratio	Protein Oncotic Pressure, Cm. H_2O	Comment
29	Acute typhlitis	Exploratory laparotomy; appendectomy	7	8	4.96	3.30	1.66	1.99	18	Patient severely distended; wound disruption on 8th day after operation; packed and strapped; acute intestinal obstruction on 11th day; emergency enterostomy proximal to obstruction by kinked loop of bowel; patient died on following day
61	Duodenal ulcer	Posterior gastroenterostomy; cholecystectomy	10	10	4.32	2.88	1.44	2.0	15	Wound disrupted on 10th day after operation; wound clean; packed and strapped; healed uneventfully
64	Chronic cholecystitis and cholelithiasis with common duct obstruction	Cholecystectomy; choledochostomy with T tube	5	9	5.92	3.64	2.28	1.60	22	Complete wound disruption on 9th day; resutured; wound healed uneventfully except for slight separation at the upper angle 9 days after resuturing
47	Acute gangrenous cholecystitis	Cholecystectomy; appendectomy	7	6	5.73	3.37	2.36	1.43	21	Complete wound disruption on 6th day; wound clean; resutured; uneventful healing
55	Chronic cholecystitis with stones in cystic duct	Cholecystectomy; exploratory duodenotomy	8	5	7.12	3.47	3.65	0.95	25	Complete wound disruption on 5th day; wound clean; resutured; uneventful healing
56	Chronic appendicitis	Appendectomy; separation of adhesions	7	5	7.17	3.60	3.57	1.01	26	Complete wound disruption on 5th day; wound clean; resutured; uneventful healing; patient had chronic cough
31	Acute cholecystitis and cholelithiasis	Cholecystectomy; separation of adhesions	9	18	6.25	3.74	2.51	1.49	23	Complete wound disruption on 18th day with discharge of biliary collection from abdomen; pneumonia on 6th day; wound resutured with drain in upper angle; uneventful healing

It can be seen from table 4 that among the patients with wound disruption the highest value for serum albumin was 3.74 Gm. per hundred cubic centimeters. All 8 patients with disrupted wounds and 10 of the 13 patients with deep wound infections had serum albumin concentrations of less than 3.75 Gm. per hundred cubic centimeters, whereas only 5 of the 23 patients with clean abdominal wounds and 3 of the 17 patients with clean hernioplasty wounds had concentrations below this level. In other words, 86 per cent of the patients with complicated wounds had serum albumin concentrations below 3.75 Gm. per hundred cubic centimeters, whereas only 20 per cent of the patients with clean wounds had such low concentrations.

TABLE 5.—*Postoperative Levels of Serum Protein Classified According to Condition of Wounds*

Classification	Protein, Gm. per 100 Cc. Serum	Albumin, Gm. per 100 Cc. Serum	Globulin, Gm. per 100 Cc. Serum	Albumin-Globulin Ratio	Protein Oncotic Pressure, Cm. H_2O
Clean hernia wounds.....	6.88 ± 0.18	4.41 ± 0.12	2.47 ± 0.12	1.89 ± 0.10	28.4 ± 0.1
Clean abdominal wounds.....	6.66 ± 0.12	4.10 ± 0.09	2.56 ± 0.11	1.76 ± 0.10	26.9 ± 0.7
Deep infection in abdominal wounds.....	5.84 ± 0.13	3.49 ± 0.10	2.36 ± 0.10	1.55 ± 0.12	21.5 ± 0.9
Disrupted abdominal wounds	6.08 ± 0.32	3.45 ± 0.07	2.63 ± 0.26	1.44 ± 0.12	21.9 ± 1.1

SUMMARY AND CONCLUSIONS

The concentrations of total protein, albumin and globulin and the calculated protein oncotic pressure of serum in the cases of 58 patients whose operative wounds were carefully observed are reported.

In general, patients who had deep infection or disruption of their wounds showed lower values for total protein and for oncotic pressure in their serum. This was due mainly to a diminution in the albumin fraction.

The occurrence of normal concentrations of serum protein and albumin in some patients with infected or disrupted wounds and relatively low concentrations in some with clean wounds implies that hypoproteinemia by itself is neither a necessary nor a sufficient condition for the development of wound infection or disruption. However, the similarity in the concentrations of total serum protein and serum albumin and in the serum protein oncotic pressures in the groups with deep infection and wound disruption suggests the idea that the poor nutritional state of which hypoproteinemia is a manifestation may favor both the development of deep infection and the disruption of clean wounds.

FUCHS TEST FOR MALIGNANCY

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The test for malignancy which is the subject of the present paper was first described in 1926.[1] It has been the object of considerable attention in Europe since that time and has served as the basis for a number of immunologic investigations by its author and others. Clinical studies have been reported on more than 1,000 cases, with an accuracy of about 90 per cent. There appears to have been no work done on it in the United States.

Fuchs observed that washed fibrin from one species of animal was not digested by serum from the same species but was digested by serum from other species. This reaction appeared to be so specific that different breeds of the same animal, e. g., rabbits,[2] could be distinguished from each other by means of it. He then investigated the reactions of pathologic blood and found that blood from patients suffering from various diseases, notably syphilis, tuberculosis[3] or malignant tumors, reacted toward blood from healthy subjects as though it were from another species of animal. Thus, the fibrin from the blood of a patient with cancer was digested by serum from a noncancerous person but not by that from another person with cancer, while serum from a subject with cancer digested the fibrin from a normal person, but did not affect fibrin from another subject with cancer. Similar results were secured with blood from patients with syphilis, tuberculosis and other

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1. Fuchs, H. J.: (*a*) Proteolytic Enzymes in Serum I, Biochem. Ztschr. **170**:76, 1926; (*b*) Proteolytic Enzymes in Serum II, ibid. **175**:185, 1926.

2. (*a*) von Falkenhausen, M.; Fuchs, H. J., and Schubul, M.: The Differences in Sera of Various Stages of Metamorphosis of Anuren, Biochem. Ztschr. **193**: 269, 1928. (*b*) Fuchs, H. J., and von Falkenhausen, M.: Proteolytic Ferments in Serum VI, ibid. **181**:438, 1927.

3. (*a*) Fuchs, H. J.: On Proteolytic Ferments in Serum IV, Biochem. Ztschr. **178**:152, 1926. (*b*) Fuchs, H.; von Falkenhausen, M., and Kowarzyk, H.: Specificity of Fibrin III, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:233, 1933. (*c*) Fuchs [1b] and von Falkenhausen.

diseases, so that false positive reactions were obtained unless precautions were taken to rule them out. It appeared that false negative reactions were rare, and hence the real value of the test lay in its ability to rule out malignancy of a tumor in doubtful cases.

In addition to the negative results (with no change in soluble nitrogen) and the positive results (with an increase in soluble nitrogen), Fuchs described a so-called "immune reaction," obtained in certain cases of infectious disease, in which there was a decrease in soluble nitrogen.[4]

Shortly after its publication, the work of Fuchs was subjected to critical examination by a number of workers. Wright and Wolf [5] studied the conditions necessary for its successful operation and reported results in 116 cases. In 45 cases of proved malignant tumor the results were positive, and no malignancy was proved in cases in which there were negative reactions. Surgical or radium therapy reversed the reaction, causing decreases in soluble nitrogen. Cadness and Wolf [6] obtained 18 positive reactions in 18 cases of proved malignant tumors. In 16 cases of benign disease they secured 5 positive reactions, 4 in cases of gastric ulcer and 1 in a case of nephritis. Yokota [7] and Van der Scheer [8] failed to confirm Fuchs's results, but their technic was imperfect.[9] Bernhard and Köhler [10] compared the Fuchs test with the lipase test, which they found to be unreliable. In 247 proved cases they reported 129 positive, 86 immune and 17 negative Fuchs reactions. In 164 cases of nonmalignant disease 9 reactions to the Fuchs test were positive, 7 were immune and 142 were negative. They found the site of the tumor to be without significance except that in cases of esophageal tumor false negative reactions were obtained. They claimed that precancerous conditions may be indicated by supposedly false positive reactions, which should always be viewed with concern. Jedlička and Weichherz [11]

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7. Yokota, K.: The Question of the Occurrence of Proteolytic Enzymes in Serum, Biochem. Ztschr. **232**:58, 1931.

8. Van der Scheer, J.: On the Action of Serum on the Fibrins of Various Species, J. Immunol. **18**:17, 1930.

9. Fuchs, H. J., and von Falkenhausen, M.: Remarks on the Work of K. Yokota Concerning the Occurrence of Proteolytic Ferments in Serum, Biochem. Ztschr. **237**:87, 1931.

10. Bernhard, F., and Köhler, K.: The Diagnosis of Cancer by the Determination of Lipase in Serums and the Ca Reaction of Fuchs, Deutsche Ztschr. f. Chir. **248**:72, 1936.

11. Jedlička, V., and Weichherz, E.: The Value of the Fuchs Test, Ztschr. f. Krebsforsch. **41**:148, 1934.

confirmed the atypical results with esophageal tumors. Of 126 cases of malignant tumor their results were incorrect in only 6. Kafka [12] obtained 90 per cent accuracy in one series and in another series of 142 cases was 94 per cent correct, using an improved technic.[13] Brandt's [14] findings were correct in 92.5 per cent of 112 cases; those of Latthammer and Rosenbohm,[15] in 72 of 77 cases. Latthammer and Pistofidis [16] compared the Fuchs and the Kahn [17] test for malignant tumor. In 28 proved cases the Fuchs test had an accuracy of 97 per cent as compared with 84 per cent for the Kahn test. In 35 cases of nonmalignant disease the Fuchs test was 97 per cent correct and the Kahn test 86 per cent. Woodhouse [18] described results in 107 cases. He was correct in 50 of 53 cases of malignant tumor and 38 of 42 of nonmalignant disease. Yasumasu [19] diagnosed early stages of carcinoma in 140 cases by the method.

The immunologic aspects of the test have been studied by Fuchs and his co-workers.[20] A rather comprehensive review of the subject [21a] to October 1935 and an article explaining the significance of the reaction were published by Fuchs.[21b]

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12. Kafka, V., Jr.: Contributions to the Study of the Fuchs Test, Ztschr. f. Krebsforsch. **41**:369, 1934.

13. Kafka, V., Jr.: Further Experiences with the Fuchs Test, Ztschr. f. Krebsforsch. **42**:241, 1935.

14. Brandt, E.: Experiences with the Fuchs Reaction, Ztschr. f. Krebsforsch. **43**:370, 1936.

15. Latthammer, R., and Rosenbohm, A.: The Fuchs Cancer Reaction, Ztschr. f. Krebsforsch. **45**:28, 1936.

16. Latthammer, R., and Pistofidis, H.: Comparison of the Diagnostic Value of the Cancer Reaction of Fuchs and Kahn, Ztschr. f. Krebsforsch. **45**:105, 1936.

17. Kahn, H.: (*a*) A Simple Flocculation Reaction of Malignant Tumor, Klin. Wchnschr. **2**:1364, 1923; (*b*) The Differential Diagnosis of Malignant Tumors with a Few Drops of Blood, ibid. **3**:920, 1924.

18. Woodhouse, D. L.: Fuchs Serum Proteolysis Test for Malignancy, Lancet **1**:138, 1937.

19. Yasumasu, T.: Serochemical Carcinoma Reaction of Fuchs, Fukuoka Acta med. **29**:157, 1936; Jap. J. M. Sc., IX, Surg., Orthop. & Odont. **5**:259, 1938.

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Modifications in the method have been suggested by Fuchs and his associates,[22] by Minibeck [23] and by Caspary,[24] as well as by Wright and Wolf.[5]

We have used the test in about 200 cases in the Vanderbilt University Hospital.

METHOD

The original method of Fuchs called for a substrate of washed fibrin, which was prepared as follows:[22c] Blood was drawn into a clean, dry syringe moistened with liquid petrolatum and was at once transferred to a tube. The fibrin was whipped out with a stick, on which it collected. It was kneaded in cold water until all pigment was washed out. The nearly white fibrin was then placed in a bag of cloth with a mesh sufficiently large to permit free access of water but small enough to retain the particles of fibrin. It was suspended in a wide-mouthed vessel in a stream of water rapid enough to keep the fibrin in constant agitation. This washing was continued for eighteen hours. The pure white product was removed from the water, washed repeatedly in distilled water and finally pressed as dry as possible with filter paper. It was then placed on the cloth, which was pinned to a board. A current of air warmed to 30 C. was directed against it, which dried it in thirty minutes. It was stored in a vacuum desiccator and remained active for at least nine months. Portions were pulverized in an agate mortar for use as required. This procedure may be modified by drying the fibrin in a vacuum desiccator instead of in a current of air and pulverizing it all for storage.

Another type of substrate was later developed, which had the advantage of furnishing larger quantities of active material from the same amount of blood. It is prepared as follows:[22a] The blood is allowed to clot spontaneously, and the serum is centrifuged off. Within ten hours after drawing, the serum is mixed with 11 volumes of 2.5 per cent trichloroacetic acid which has been warmed to 20 C. The precipitate is thrown down but not packed, and the supernatant fluid is poured off. Fresh trichloroacetic acid solution at a temperature of less than 15 C. is added, and the precipitate is stirred into it. The centrifugation is repeated and the fluid is decanted five times. The last time, the precipitate is packed. After the supernatant fluid is poured off, the vessel and the surface of the precipitate are rinsed with distilled water to remove the residual wash fluid, but the precipitate is not disturbed. Water is carefully poured into the vessel without disturbing the precipitate, and the centrifugation is repeated at high speed to squeeze out the residual acid. This is performed three times, the excess fluid being allowed to drain off thoroughly after the last time.

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22. (*a*) Fuchs, H. J.: A New Substrate for the Examination of Blood for Malignant Tumors, Klin. Wchnschr. **11**:1997, 1932. (*b*) Fuchs, H. J., and von Falkenhausen, M.: A New Micro Method for the Determination of Nitrogen and Its Application to the CaR, Biochem. Ztschr. **245**:304, 1932; (*c*) Further Contributions to the Serum Chemical Diagnosis of Malignant Tumors (CaR), Ztschr. f. d. ges. exper. Med. **81**:169, 1932.

23. Minibeck, H.: New Technic for the Fuchs Reaction for the Diagnosis of Cancer, Ztschr. f. d. ges. exper. Med. **96**:362, 1935.

24. Caspary, H.: An Improved Method for the Fuchs Cancer Reaction, Ztschr. f. Immunitätsforsch. u. exper. Therap. **82**:506, 1934.

The solid product is finally transferred, as completely as possible to a glass plate, and the plate, centrifuge vessel and spatula are placed in an oven at not over 40 C. for three hours. The material from all the utensils is then scraped onto a clean piece of paper and left in the oven overnight. It is finally ground in an agate mortar and stored in the ice box.

Fuchs emphasized the importance of testing each new preparation (1) against normal serum to prove its inactivity against such serum and (2) against foreign serum to determine its activity against this. These tests should never be omitted and, according to our experience, should be repeated at frequent intervals.[25]

The test is carried out as follows: Enough blood to give 5 cc. of clear serum is drawn in a clean, dry syringe lubricated with liquid petrolatum to prevent hemolysis. It is allowed to clot spontaneously and is then centrifuged. The serum is transferred to a clean, dry test tube.

The next step, the incubation of serum with substrate, may advantageously be carried out in a test tube of more than 12 cc. capacity and strong enough to withstand centrifugation. The usual type of pointed centrifuge tube should not be used, because the solid substrate collects in a mass in the tip, exposing a minimal surface to the serum. A test tube may be used, but the supernatant fluid from the subsequent trichloroacetic acid precipitation may have to be filtered. We have used ordinary 150 mm. pyrex test tubes with a constriction made at the level of the surface of the trichloroacetic acid precipitate.

For each test four tubes are required. Into each of two of them approximately 5 mg. of powdered substrate is measured with a small glass scoop. One cubic centimeter of serum is accurately measured with an Ostwald pipet into each of the four tubes and is thoroughly mixed with substrate. The tubes are then set in a beaker or other convenient vessel, covered with a watch glass or a Petri dish and placed in an incubator at 38 C. overnight. Fuchs placed chloroform in the oven to reduce the bacterial growth.

The next day 11 cc. of 5 per cent trichloroacetic acid is accurately measured from a buret into each tube and after thorough mixing is allowed to stand for fifteen minutes. The tubes are then centrifuged, and the supernatant fluid is decanted into clean, dry test tubes. Samples of 4 cc. each are pipetted into digestion tubes for the estimation of nitrogen by a micro-Kjeldahl procedure. Increases of over 2 mg. per hundred cubic centimeters in the substrate tubes indicate a positive reaction.

Although in the work reported here we used all the precautions specified by Fuchs, we since have used chemically clean, but not sterile, technic, have omitted chloroform from the incubator and have never encountered difficulty from microbial contamination. The quantities used are those recommended by Fuchs but may be varied to suit conditions, e. g., 14 cc. of trichloroacetic acid may be added to the serum and 5 cc. aliquots taken for analysis. Filtration may, of course, be substituted for centrifugation of the trichloroacetic acid precipitate. We have found that an incubation period of twelve to eighteen hours gives the best results. Shorter periods give smaller differences, due to incomplete action of the enzyme; other reactions assume significance with longer ones.

The accuracy and delicacy of the nitrogen determination are the crux of the whole procedure. Several methods have been advocated. We have used the manometric one of Van Slyke, though others are doubless as good.[26]

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25. Fuchs and von Falkenhausen.[9] Van der Scheer.[8] Yokota.[7]
26. Kafka.[12] Kahn.[17b] Minibeck.[23]

RESULTS

We obtained negative reactions in the cases of 74 patients in whom no evidence of a malignant process was found. These included 4 patients with syphilis and 4 with tuberculosis. There were 3 samples of placental blood and 10 samples of blood from patients in the fourth to the seventh month of pregnancy.[16] In 10 cases malignant tumor was suspected but the growth was shown on biopsy to be benign. There were a number of negative values corresponding to Fuchs's "immune reaction," most of which were too small to be significant. Of those which were greater than experimental error, 2 were given by blood from tuberculous patients, 1 by blood from a syphilitic patient and 3 by placental blood or blood from pregnant women.

In 56 cases of proved malignant tumor the Fuchs reaction was positive. This series included 11 cases of carcinoma of the cervix, 9 cases of cancer of the bladder and 3 each of malignant tumor of the face, stomach, breast and jaw. Other growths represented were tumors of the brain, cancer of the ovary, hand, tongue, prostate and pancreas.

The chief interest in these results lies in the wide variety of tumors that give positive reactions. Previous reports in the literature indicate that only esophageal lesions fail to give positive reactions. Why this particular site differs from all others is not known, and further experiment might show this statement to be inaccurate.[27] One case of syphilis is included, but the positive reaction was probably due to the accompanying malignant growth. In 2 cases the growths were recurrent after one to four years.

From the standpoint of evaluating the method the figures in the accompanying table are perhaps the most important, since they indicate the conditions under which it fails. The blood in all cases tabulated gave negative reactions by the Fuchs method, though the patients either had or had previously had proved malignant tumors. By far the greatest number of patients represented in this table had undergone some sort of therapy, after which the tumor showed no signs of recurrence. In other words, as far as could be judged clinically they were cured.

If the assumption is made that the Fuchs reaction would have been positive prior to treatment, it would seem that the effects of therapy are rather prompt, as has been suggested by other investigators.[28] In case 5 a negative reaction was obtained six days after operation. In case 195 the reaction was negative a week after operation. In several negative reactions were obtained after two or three months. Case 147 is particularly interesting in this connection. The patient was given radium on May 26, 1937. On July 28 her blood gave a positive Fuchs reaction. She was operated on three days later. High voltage roentgen therapy

27. Bernhard and Köhler.[10] Jedlička and Weichherz.[11]
28. Cadness and Wolf.[6] Wright and Wolf.[8]

Negative Fuchs Reactions in the Presence of Malignant Tumor or a Past History of Malignant Tumor

No.	Clinical Diagnosis	Comment	Residual Nitrogen, Mg./100 Cc. of Blood: Serum Alone	Serum and Substrate	Difference
		A. Disagreement Explainable			
5	Sarcoma of jaw	6 days after operation	30.89	31.09	0.20
5	Sarcoma of jaw (same case*)	3 weeks after operation	23.13	23.72	0.59
24	Carcinoma of larynx	Roentgen therapy 2 months previously	20.52	20.76	0.24
27	Carcinoma of lip and neck	Roentgen therapy 19 months and operation 14 months before; no recurrence	31.10	31.24	0.14
29	Carcinoma of lip	Operation 1 month before; roentgen therapy in progress	24.42	25.56	1.14
37	Squamous cell carcinoma of cervix	Operation and roentgen therapy 5 weeks before	17.32	17.57	0.25
39	Carcinoma of ear	Roentgen therapy 2 months before; no recurrence	31.14	31.00	−0.14
40	Carcinoma of cervix	Operation and roentgen therapy 2 months before	26.26	26.36	0.10
43	Epithelioma of face	Only 5 weeks' duration	31.27	31.59	0.32
49	Carcinoma of mouth	Operation 6 months before	29.38	29.09	−0.29
57	Carcinoma of face	Only 4 weeks' duration	28.93	29.00	0.07
64	Carcinoma metastatic from breast	Operation 2 years and roentgen therapy 3 months previously	24.67	24.57	−0.10
70	Carcinoma of lip	Operation 16 months before; recurrence 4 months after this test	35.01	34.71	−0.30
71	Carcinoma of lip	Operation and roentgen therapy 7 months ago	40.86	40.14	−0.72
79	Carcinoma of cervix	Radium and operation 2 months ago	23.01	22.75	−0.26
82	Carcinoma of lip	Only 3 months' duration	34.84	35.20	0.36
83	Carcinoma of cervix	Roentgen therapy in progress	26.20	26.03	−0.17
123	Carcinoma of bladder	Roentgen therapy	36.37	35.98	−0.39
136	Carcinoma of breast	Extensive carcinomatosis of long standing but in remisison	26.11	26.22	0.11
137	Melanoma of vulva	2 years old but only 4 months of rapid growth	24.35	24.54	0.19
140	Carcinoma of face	Roentgen therapy	31.89	32.67	0.78
147	Squamous cell carcinoma of cervix	2 weeks after operation (positive before operation)	27.44	27.22	−0.22
159	Adenocarcinoma of uterus	Radium and roentgen therapy 8 years ago	23.99	25.09	1.10
168	Squamous cell carcinoma of cornea	Only 4 months' duration	34.31	35.60	1.29
175	Carcinoma of esophagus		21.27	21.08	−0.19
180	Carcinoma of penis	Three weeks after operation	36.83	36.57	−0.26
191	Carcinoma	12 days after exploratory laparotomy	36.81	37.24	0.43
195	Adenocarcinoma	1 week after operation	49.51	49.45	−0.06
	Total, 27 cases				
		B. Disagreement Not Explainable			
23	Basal cell carcinoma of arm and squamous cell carcinoma of ear		24.51	24.69	0.18
32	Lymphatic leukemia		27.64	28.00	0.36
47	Carcinoma of lungs		35.91	35.49	−0.42
128	Monoblastic leukemia		26.98	26.49	−0.49

Negative Fuchs Reactions in the Presence of Malignant Tumor or a Past History of Malignant Tumor—Continued

No.	Clinical Diagnosis	Comment	Residual Nitrogen, Mg./100 Cc. of Blood		
			Serum Alone	Serum and Substrate	Difference
133	Carcinoma of prostate		24.78	25.73	0.96
145	Carcinoma of prostate		50.44	51.84	1.40
152	Adenocarcinoma of cecum		51.61	51.92	0.31
157	Carcinoma of face		24.59	24.90	0.31
171	Adenocarcinoma		33.89	34.53	0.64
174	Carcinoma of testes		30.03	31.74	1.71
182	Carcinoma of rectum		19.42	20.76	1.34
183	Carcinoma of ovary	Recurrence 4 years after operation	25.71	25.97	0.26
183	Carcinoma of ovary (same case*)	24 hours after roentgen therapy	24.53	25.90	1.37
185	Benign hypertrophy of prostate	Malignant at autopsy	99.41	99.57	0.16
187	Carcinoma of cervix		30.33	30.65	0.32
188	Carcinoma		41.52	42.01	0.49
190	Squamous cell carcinoma of cervix		21.33	21.29	—0.04
192	Secondary carcinoma of pelvic bones	Recurrence 9 months after operation	44.45	45.38	0.93
198	Wilms' embryoma		24.93	25.35	0.42
	Total, 18 cases				

* Cases in which a negative reaction was twice obtained are included only once in computing the total number of cases.

was then given and was repeated beginning December 13. On Feb. 15, 1938 her blood still gave a positive reaction. On March 1 it gave the negative reaction reported in the table. At this time and one week later she was much improved. She did not return to the hospital. She died June 15 in another city, of "locked bowels." That the test measures the activity of the malignant growth is indicated by case 136. On admission the patient was found to have extensive carcinomatosis with metastases to the bones and other structures. At this time her blood gave a positive Fuchs reaction. She was pregnant and was delivered by cesarean section, receiving several transfusions but no treatment for the malignant tumor. Two months later she returned to the hospital. Blood was taken and gave the negative reaction recorded in the table. At this time she was much improved; she had gained weight, and there was marked retrogression of her osseous lesions. Several months later, however, she died.

A third case indicating that operative procedure alone may affect the result was observed (case 191). The blood gave a positive Fuchs reaction on July 29, 1938. An exploratory laparotomy was performed when a biopsy specimen was taken, but nothing more was done. On August 10 a second sample of blood was taken, which gave the negative result reported in the table.

In case 175 the growth was a carcinoma of the esophagus, which, as has been stated, is said to be associated with a negative reaction of the blood.

In 4 of the cases reported the growths were respectively of four weeks', five weeks', three months' and four months' duration, the onset being pretty accurately determinable because of the superficial character of the growth. In a fifth, although the growth was about two years old, it had shown rapid growth only during the four months preceding the examination. The false negative reactions may, therefore, be explained by the assumption that the production of enzymes does not reach a detectable level for over five months. A similar case (not included in this group because no microscopic examination was made, though the diagnosis is probably correct) adds weight to this assumption. There are 27 examples in the table (section *A*) of patients who were cured, were under treatment or had lesions in the early stages of growth.

There remain in this group (section *B* of table) 18 cases in which no explanation appears and in which the results of the Fuchs test must be assumed to be genuine false negative reactions.

In 5 other cases the Fuchs reaction was positive in spite of the fact that the pathologists failed to find malignant tissue. This, of course, does not mean that such tissue was not present in some other part of the body.[10]

We also have data on 13 cases in which no microscopic examination was made.

Other investigators have reported that false negative reactions are seldom obtained but that false positive reactions may be obtained in a number of conditions, notably syphilis and tuberculosis. Our experience has not confirmed this. We have had no positive results from either of these diseases and have obtained more false negatives than false positive reactions. From experiences subsequent to the completion of this work, we feel that the accuracy of the method could be materially increased by improving the quality of the substrate and by frequent checking of its activity. The fact that this was not done may account for a number of our failures. After completion of this work no tests with old substrate were made for several weeks when a negative result was obtained in a proved case of malignant tumor. Investigation revealed that all samples of substrate had become inactive. Since that time we have been unable to prepare an active trichloroacetic acid substrate, though active fibrin ones have been prepared consistently. The explanation for this failure has not yet been found. We suspected poisoning of the enzyme by traces of heavy metals in the reagents, but using water redistilled from glass to make up all solutions and to recrystallize the trichloroacetic acid did not change the results.

The mechanism of the reaction is still obscure and should be studied. Apparently, the substrate participates in the reaction in an active way. If it does serve merely as a protein on which serum protease acts, it must be an unstable one which can change on standing.

SUMMARY

The Fuchs test for malignancy is a chemical laboratory procedure which can be performed with 15 cc. of blood. Although there is a strong correlation between the results of this test and the pathologic observations, it apparently has certain limitations: 1. The growth must be over six months old; (2) the patient should not have been operated on or have received radium or roentgen treatment for at least a month, and (3) the tumor must be in a period of active growth.

Dr. Henry Douglas, Dr. J. C. Pennington and other members of the staff of Vanderbilt University Hospital supplied the clinical material for this work.

BACILLUS PYOCYANEUS OSTEOMYELITIS OF THE SPINE

REPORT OF A CASE OF SUCCESSFUL TREATMENT WITH SULFANILAMIDE

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The case to be presented is unique for several reasons. It is the first case of osteomyelitis due to Bacillus pyocyaneus to be reported in the literature. It is the only case of spinal skeletal involvement by this organism which could be found. Finally, it is one of the few cases in which sulfanilamide therapy was tried and appeared effective.

The literature on infections due to B. pyocyaneus (Pseudomonas aeruginosa) has been reviewed in detail in several papers in the past twenty-five years.[1] No effort will be made to repeat this work. The organism is not uncommonly encountered in infected wounds of various types, especially large granulating areas. Ordinarily it is only slightly pathogenic, is easily controlled by applications of boric acid and presents no problem. It is recognizable by its color and odor. Occasionally, however, it becomes a dangerous pathogen, invading visceral cavities, mucous membranes and even the blood stream, with secondary localizations.

Infections of the genitourinary tract are especially likely to be due to this bacillus. In a recent discussion of a case of B. pyocyaneus meningitis, Slutsky and Matlin[2] reviewed the incidence of invasion of the blood stream following manipulations of the genitourinary tract. They reported that when routine cultures of the blood were made in

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From the Orthopedic Service of Drs. R. K. Lippman and S. Selig and the Medical Service of Dr. B. S. Oppenheimer, the Mount Sinai Hospital.

1. (*a*) Epstein, J. W., and Grossman, A. B.: Bacillus Pyocyaneus Infections in Children, Am. J. Dis. Child. **46**:132 (July) 1933. (*b*) Brown, C. F. C.: Bacillus Pyocyaneus Infections, M. Clin. North America **14**:1243 (March) 1931. (*c*) Fraenkel, E.: Weitere Untersuchungen über die Menschenpathogenität des Bacillus pyocyaneus, Ztschr. f. Hyg. u. Infektionskr. **84**:369, 1917.

2. Slutsky, N., and Matlin, P.: Pyocyaneus Meningitis, J. A. M. A. **113**: 1400 (Oct. 7) 1939.

investigation of chills after such instrumentation, Scott [3a] found 3 of 82 "positive" cultures yielding B. pyocyaneus, while Hyman and Edelman [3b] reported 1 of 63 "positive" cultures as yielding this organism. In addition, individual cases of infection with a similar portal of entry have been reported by others.[3c] In adults this is probably the most common source of entry of the organism, others being by way of the gastrointestinal tract and by way of discharging surgical wounds. In children general infection usually arises from involvement of the skin in the form of ecthyma, as reported by Epstein and Grossman.[1]

Lesions of the skeletal system caused by this organism have rarely been reported, as compared with frequent reports of pyelitis, ecthyma and meningitis. Epstein and Grossman mentioned 2 cases of suppurative arthritis. One was a case of sepsis of the hip, published by Groves [4] in 1909; the condition was successfully treated by incision and drainage with use of autogenous vaccine. The other was a case of a suppurating knee which required amputation, reported by Wassermann [5] in 1901. In 1927, Pinelli [6] described a case of suppuration of the left shoulder; in this case also the condition was cured by incision and drainage combined with use of autogenous vaccine. Finally, Bishop [7] recently reported a case of suppurative arthritis of the ankle due to direct invasion by B. pyocyaneus from pyoderma in an extensive burn. In this case, again, the condition was cured by incision and drainage of the ankle and use of autogenous vaccine. No case of hematogenous osteomyelitis due to this organism has been discovered.

Until recently there has been no acceptable specific therapy for systemic infection by B. pyocyaneus. Autogenous vaccines have been used for many years, almost since discovery of the pathogenic properties of the germ. Fraenkel,[1c] in 1917, in an exhaustive review of 26 cases, stated that autogenous vaccines are of little use, since 83 per cent of the

3. (*a*) Scott, W. W.: Blood Stream Infections in Urology: Report of Eighty-Two Cases, J. Urol. **21**:527 (May) 1929. (*b*) Hyman, A., and Edelman, L.: Medical and Surgical Aspects of Hematogenous Infections in Urology, ibid. **28**: 173 (Aug.) 1932. (*c*) Barrington, F. J. F., and Wright, H. D.: Bacteremia Following Operations on Urethra, J. Path. & Bact. **33**:871 (Oct.) 1930. Powers, J. H.: Renal Function Following Trauma of Kidney: Clinical and Experimental Study, New York State J. Med. **36**:1411 (Oct. 1) 1936. Ewell, G. H.: Bacillus Pyocyaneus Bacteremia Secondary to Pyelonephritis and Prostatic Abscess with Death: Case Report, Urol. & Cutan. Rev. **40**:697 (Oct.) 1936.

4. Groves, E. H.: A Clinical Lecture on a Case of Bacillus Pyocyaneus Pyaemia Successfully Treated by Vaccine, Brit. M. J. **1**:1169, 1909.

5. Wassermann, A.: Septische Nabel-Infection Neugeborener: Ein Beweis für die B. Pyocyaneus beim Menschen, Virchows Arch. f. path. Anat. **165**:342, 1901.

6. Pinelli, A.: Artrite monoarticulare primitiva da piocianeo, Pediatria **35**: 147 (Feb. 1) 1927.

7. Bishop, W. A., Jr.: A Case of Primary Bacillus-Pyocyaneus Arthritis in an Infant, J. Bone & Joint Surg. **20**:216 (Jan.) 1938.

infections end fatally, despite publication of occasional individual successes in treatment. Soeters,[8] in 1937, first reported a case of sepsis due to this organism treated with a derivative of sulfanilamide ("prontosil soluble," now known as azosulfamide; disodium sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′ disulfonate) and repeated blood transfusions; recovery occurred. Stewart and Bates[9] thereafter pointed out that others of the same family of organisms, such as Bacillus typhosus and Bacillus coli, are susceptible to the action of sulfanilamide in animals and probably in human beings. They reported a case of infection of the gastrointestinal and urinary tracts successfully treated by the drug. Helmholz[10] and Long and Bliss[11] have mentioned the efficacy of sulfanilamide in clearing the urine of B. pyocyaneus. The latter authors have estimated that a urinary concentration of sulfanilamide of 300 mg. per hundred cubic centimeters is required to sterilize the urine of this organism.

REPORT OF CASE

A 56 year old Irishman, single, was admitted to the medical service of Dr. B. S. Oppenheimer at the Mount Sinai Hospital on May 28, 1938 and discharged October 4.

In his youth he had had infectious disease of the right hip with a discharging sinus for over two years. This had become and remained quiescent, with fibrous ankylosis of the joint. On two occasions, ten and five weeks respectively before admission, the patient had attacks of colicky pain in the right loin, radiating to the right pubic region, relieved by hypodermic medication after several hours and unaccompanied with hematuria, chills or fever. Because of this he was examined for renal calculi, and the cystoscope was used eight days before admission. On the next day he vomited and had severe pain in the loin and high fever. Prostration was marked for a week. On the day before admission he had a severe shaking chill, a temperature of 106 F. and delirium. There was a little pain in the right loin at the time of admission.

Physical Examination.—The patient was well developed and acutely ill. The heart and lungs were normal; the abdomen was soft. Bilateral tenderness in the costovertebral angles was present, more marked on the right. The prostate gland was moderately and diffusely enlarged. The left hip was stiff, with much atrophy of the surrounding muscles but no localized tenderness or pain. There were two small healed scars on its outer aspect.

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8. Soeters, J. M.: Pyocyaneus Sepsis in a Child: Recovery with Prontosil, Maandschr. v. kindergeneesk. **7**:74 (Nov.) 1937.

9. Stewart, W., and Bates, T.: Bacillus Pyocyaneus Infections: A Case Treated with Sulfanilamide, Lancet **1**:820 (April 8) 1939.

10. Helmholz, H. F.: Bactericidal Power of Urine After Administration of Prontylin by Mouth, Proc. Staff Meet., Mayo Clin. **12**:244 (April 21) 1937.

11. Long, P. H., and Bliss, E. A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939.

Early Laboratory Data.—The value for hemoglobin was 71 per cent. The red blood cells numbered 4,800,000 per cubic millimeter. The white blood cells numbered 10,100 per cubic millimeter, with 90 per cent polymorphonuclear leukocytes, showing marked toxic granulation.

The urine was alkaline; the specific gravity was 1.015. There was a trace of albumin. Microscopic examination showed red and white blood cells, and there was a pure culture of B. pyocyaneus.

The Wassermann reaction of the blood was negative, and the value for blood urea was 31 mg. per hundred cubic centimeters. A culture of blood taken on admission was sterile after four days.

Roentgen examination of the abdomen (genitourinary flat plate) showed a left renal calculus and a second small concretion on the right side, near the pelvic

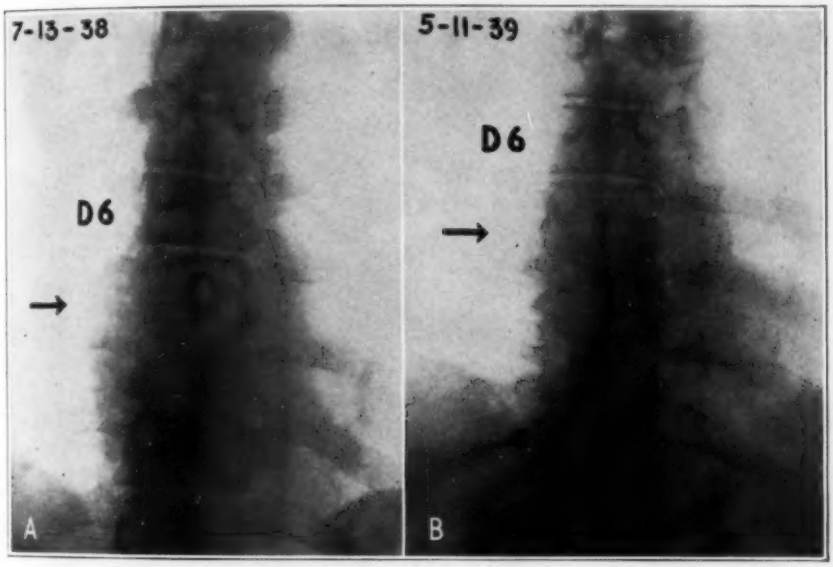

Fig. 1.—Lateral view of the dorsal portion of the spine, showing the course of infection (*A* and *B*) and the final fusion (*C*).

rim, in the course of the ureter. The left hip gave evidence of old quiescent destructive osteoarthritis. The thoracic film showed a bilaterally elevated diaphragm, with a linear shadow of atelectasis above the left leaf.

Examination and culture of material from the stool gave negative results.

Diagnosis.—The patient was assumed to have pyelonephritis and possibly prostatitis (following use of the cystoscope) with left renal and right ureteral calculi. The chills and fever were considered to be due to invasion of the blood stream by some organism, to be identified.

Course of Infection.—Administration of large quantities of fluids, a purgative dose of castor oil and citrates was begun at once. Four grams of sulfanilamide was given daily. This dose was later reduced, and administration of the drug was stopped after nine days, when a total of 27 Gm. had been given. The temperature,

which rose to 106 F. shortly after admission, "spiked" from 99 to 106 F. for two days and then dropped to practically normal. The patient became anorectic, depressed and slightly disoriented, which was the cause for discontinuing the medication.

One and one-half weeks after admission, pain in the back was present when the patient raised himself in bed, and exquisite tenderness was elicited over the lower dorsal segments of the spine. Tenderness of the costovertebral angles was minimal. The temperature, which had been normal for some time after discontinuance of sulfanilamide therapy, began to rise irregularly to from 102 to 103 F. daily, and the patient again appeared acutely ill. Although it was the general suspicion that a metastatic focus had lodged in a dorsal vertebra, it was some weeks before roentgen confirmation was obtained. Two separate roentgen examinations, on June 6 and 24, showed no changes in the dorsolumbar portion of the spine other than mild hypertrophic arthritis.

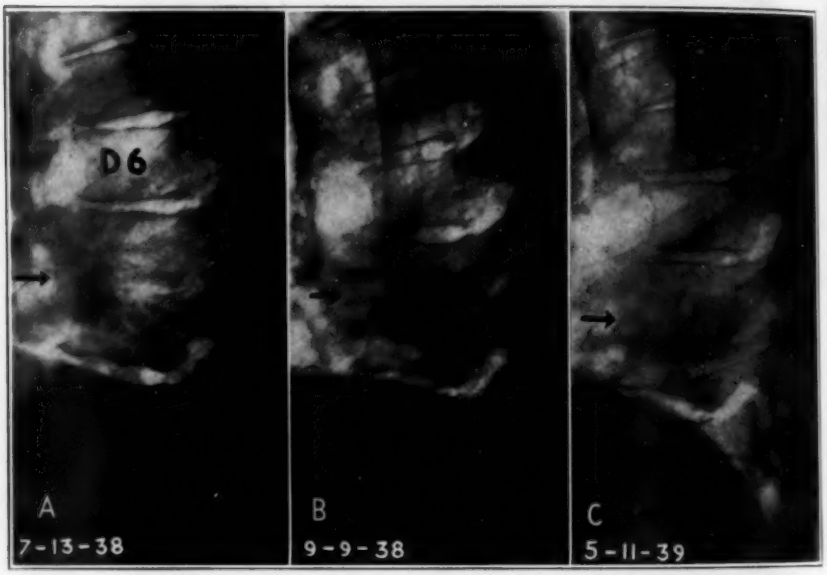

Fig. 2.—Anteroposterior views of the dorsal portion of the spine. *A* shows the lesion between the seventh and the eighth dorsal vertebra; *B*, the final fusion.

Repeated cultures of the urine, on June 1, 4, 6, 11, 20 and 27 and July 31, as well as later (on August 25), all yielded B. pyocyaneus. A second culture of blood, taken in June 27, during a rise in temperature above 102 F., showed a pure growth of B. pyocyaneus in one flask. The sedimentation rate was 18 mm. in twenty minutes, indicating the activity of the general infection. Chemical study of the blood on June 22 showed a carbon dioxide–combining power of 54.9. The value for calcium was 9.8 mg., that for phosphorus 3.6 mg., that for urea 32 mg. and that for sugar 75 mg. per hundred cubic centimeters. On July 7 the value for blood urea was 7 mg. per hundred cubic centimeters, and the icteric index was 9. An intravenous pyelogram taken on June 28 showed the left calculus in the ureter and the right one low in the ureter.

Sulfanilamide was administered again when the infection could not be controlled (from July 5 to 10 inclusive), in larger doses than before, a total of 34 Gm. being given. The temperature subsided and remained low for the remainder of the patient's stay in the hospital. Acidification with large doses of mandelic and gluconic acids was tried in an attempt to sterilize the urine, but pyuria and pyocyanuria persisted despite a p_H of 5.2. Two transfusions of citrated blood, 500 cc. each, were given to combat the anemia after the value for hemoglobin fell as low as 52 per cent.

As local tenderness over the lower dorsal segments of the spine grew more definite, root zones of cutaneous hyperesthesia appeared. On July 13, seven weeks after the first clinical evidence of sepsis, new roentgenograms of the dorsal portion of the spine showed narrowing of the seventh dorsal interspace, with definite erosion of the adjacent cortical plates of the seventh and eighth dorsal vertebral bodies. There was suggestive widening of the mediastinal structures at this level, probably due to a soft tissue abscess or to infiltration. It was now evident that the patient had acute osteomyelitis of the dorsal portion of the spine, secondary to urosepsis. A gibbus was noted at the eighth dorsal vertebra, and consultation with an orthopedist resulted in the decision that an operation was unwarranted in view of amelioration of the symptoms by sulfanilamide.

A plaster jacket was applied on July 20, and the pain immediately subsided. The remainder of the stay in the hospital was uneventful, the patient being kept recumbent almost to the time of discharge, when he was transferred to the Montefiore Hospital for Chronic Diseases for convalescent care. The value for hemoglobin was 70 per cent on his discharge, and a congo red test showed no evidence of amyloidosis. Further roentgen studies of the dorsal portion of the spine on September 6 and 9 showed an increase in size of the paravertebral mass with further destruction of the opposing vertebral surfaces.

At the Montefiore Hospital, convalescence continued uneventfully. The patient stayed there from October 4 to April 23, 1939. Culture of the urine continued to show B. pyocyaneus, and a ureteral calculus was still visible on the left side. The plaster jacket was worn for several months and then was replaced by a high Knight spinal brace. The patient was ambulatory and had very few symptoms at the time of discharge.

On May 11 the patient appeared at the Mount Sinai orthopedic follow-up clinic and was found to be clinically well, with good motion of the spine.

Roentgen examination showed disappearance of the intervertebral space between the seventh and eighth dorsal vertebrae, as well as of the soft tissue shadow. In September, fusion of the involved vertebral bodies was considered solid, and the brace was finally discarded. There was no local tenderness, but slight residual gibbus and occasional local pain were present.

COMMENT

The diagnosis of B. pyocyaneus urosepsis following cystoscopic procedures for renal calculus, complicated by B. pyocyaneus osteomyelitis of the dorsal portion of the spine, would seem to be established by the septic picture, the repeated pure cultures of the organism from the urine and, above all, the blood culture yielding the same organism, which can hardly have been a contaminant. Nevertheless, at the time of transfer, the possibility of Pott's disease following childhood tuberculosis of the hip was considered, the urinary sepsis then being inter-

preted as incidental. Against this are the rapid response of the febrile infectious picture to administration of sulfanilamide and the course of the spinal infection. Healing of the lesion of the dorsal portion of the spine in a year and a half by fusion of the involved vertebrae with good calcification is unlike Pott's disease but is compatible with infectious osteomyelitis due to a pyogenic organism.

SUMMARY

It is shown that the ordinarily saprophytic B. pyocyaneus may under certain circumstances become pathogenic and invasive and may cause septicemia with secondary localization.

In adults, one of the most common portals of entry is by infection of the urinary tract, especially after operation or other instrumentation.

A case is reported in which this occurred with secondary localization in the dorsal portion of the spine. This is the first case of B. pyocyaneus osteomyelitis to be reported in the literature.

It took seven weeks, during which there were negative results on two examinations, to demonstrate the suspected spinal lesion roentgenographically.

Sulfanilamide controlled the original sepsis but did not prevent localization in the spine.

Further administration of sulfanilamide controlled the sepsis, which had recurred.

Subsequent treatment by orthopedic measures resulted in healing by fusion of the spine in less than one and one-half years.

INCOMPLETE INDIRECT INGUINAL HERNIAS

A STUDY OF 2,462 HERNIAS AND 2,337 HERNIA REPAIRS

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A study was made of all hernias in patients admitted to the wards of St. Luke's Hospital, New York, from 1926 to 1935 inclusive. Also included in the study were all hernias repaired from 1916 to 1925 inclusive which were observed postoperatively for nine months or longer. This gave a total of 4,442 hernias, of which 2,462, or 55.4 per cent, were incomplete indirect inguinal hernias. They made up 67.4 per cent of all inguinal hernias included in the study.

Of these 2,462 hernias, 2,337 were repaired. Among the 1,668 which were followed for nine months or longer (the average follow-up time was thirty-six months), 120 recurrences were found, an incidence of 7.2 per cent. The average time after operation at which these recurrences were first noted was thirty-two and two-tenths months.

ETIOLOGIC FACTORS

Age at Onset.—The age at which the hernia was first noted must of necessity be taken as the closest possible approximation of the patient's age at the time of development of the hernia. In this series of cases this figure varied between 1 day and 75 years, the average being 30.9 years.

For the first three five year periods of life the incidences were between 4.3 and 6.5 per cent, increasing to 8.4 per cent between the fifteenth and the twentieth year. The five year groups between the ages of 20 and 40 years showed approximately the same incidences, varying between 10.8 and 12.7 per cent. Following these incidences, the four greatest, the incidences decreased gradually with each five year period to 0.3 per cent for each of the two between the ages of 65 and 75 years.

Grouped into twenty year periods of life, the incidences were: first period, 23.6 per cent; second, 46.9 per cent; third, 27.5 per cent, and fourth, 2.5 per cent.

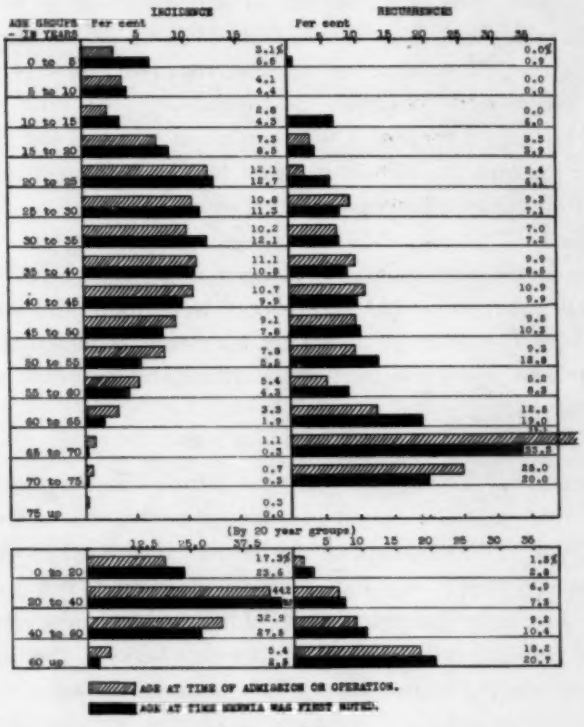
Recurrence rates increased with increase in the age of the patients at the time the hernias were first noted. For the first twenty years of life the recurrence rate was 2.8 per cent; from the age of 20 to 40 years,

From the Surgical Services of St. Luke's Hospital.

7.3 per cent; from 40 to 60 years, 10.4 per cent, and from 60 to 75 years, 20.7 per cent.

Age at Admission or Operation.—The age of the youngest patient at the time of admission or operation was 1 day, and that of the oldest, 93 years. The average age was 34.8 years.

Only 17.3 per cent were admitted or operated on in the first twenty years of life, and in this group the recurrence rate was 1.3 per cent. Nearly half (44.2 per cent) were admitted or operated on between the



Age incidence.

ages of 20 and 40, with a recurrence rate of 6.9 per cent; 32.9 per cent between 40 and 60, with a recurrence rate of 9.2 per cent; and 5.3 per cent between 60 and 80, with 20 per cent of recurrences.

Sex.—The incidence of males in this group of cases of incomplete indirect inguinal hernia was 88.7 per cent and that of females 11.3 per cent. This is explained by the differences in shape of the male and female pelves, the presence of the spermatic cord in the male and the much greater incidence of strenuous occupations among males.

The same factors account for the difference in the recurrence rates, which were 7.5 and 4.9 per cent respectively. Difficulty in getting

employed men to leave their work to come in for follow-up examinations was the reason that a somewhat larger percentage of women were examined postoperatively.

Race.—The relative incidence of the three races (table 4) in the group of patients covered by this study is no indication of the relative frequency with which hernias occur among those races. Instead, the figures approximate closely their proportions among the general admissions to the hospital.

TABLE 1.—*Age at Which Hernia Was First Noted*

Age Group (in Years)	Total Hernias	Per Cent of Entire Group		Number Followed Post-operatively	Number of Recur-rences	Per Cent Recurrences	
0 to 5	159	6.5		112	1	0.9	
5 to 10	169	4.4	23.6	75	0	0.0	2.8
10 to 15	106	4.3		83	5	6.0	
15 to 20	208	8.4		152	6	3.9	
20 to 25	312	12.7		212	13	6.1	
25 to 30	288	11.3	46.9	198	15	7.1	7.3
30 to 35	298	12.1		194	14	7.2	
35 to 40	265	10.8		179	15	8.5	
40 to 45	244	9.9		162	16	9.9	
45 to 50	192	7.8	27.5	126	13	10.3	10.4
50 to 55	125	5.5		86	11	12.8	
55 to 60	97	4.3		60	5	8.3	
60 to 65	44	1.9		21	4	19.0	
65 to 70	7	0.3	2.5	3	1	33.3	20.7
70 to 75	8	0.3		5	1	20.0	
Totals	2,462	100.0	100.0	1,603	120	7.2	7.2

The average age of the patients when incomplete indirect inguinal hernias were first noted was 30.9 years.

That the incidence of recurrences should be less among Negroes than among white patients, 4.9 per cent as compared to 7.5 per cent, is of interest and possibly can be accounted for by the fact that the average Negro patient has better muscular development than has the average white patient. On the other hand, the relatively small number of repairs done on Negro patients may not have given a true picture of the incidence of recurrence in this race.

Trauma.—The accuracy of a history of definite trauma as an etiologic factor in the development of incomplete indirect inguinal hernias must rest to a large degree on conjecture. Unless a patient has been

TABLE 2.—*Age at Admission or Operation*

Age Group (in Years)	Total Hernias	Per Cent of Entire Group		Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences	
0 to 5	76	3.1		52	0	0.0	
5 to 10	102	4.1	17.3	73	0	0.0	1.3
10 to 15	70	2.8		49	0	0.0	
15 to 20	179	7.3		125	4	3.3	
20 to 25	298	12.1		207	5	2.4	
25 to 30	266	10.8	44.2	172	16	9.3	6.9
30 to 35	252	10.2		172	12	7.0	
35 to 40	282	11.1		199	19	9.9	
40 to 45	263	10.7		174	19	10.9	
45 to 50	225	9.1	32.9	158	15	9.5	9.2
50 to 55	185	7.8		129	12	9.3	
55 to 60	131	5.3		94	5	5.2	
60 to 65	82	3.3		48	6	12.5	
65 to 70	26	1.1	5.3	9	5	55.5	20.0
70 to 75	17	0.7		8	2	25.0	
75 to 80	4	0.2		0	..	...	
80 to 85	3	0.1		1	0	0.0	
85 to 90	0	0.0	0.14	..	..	...	0.0
90 to 95	1	0.04		0	..	...	
Totals	2,462	100.0	100.0	1,668	120	7.2	7.2

The average age at the time of admission or operation for incomplete indirect inguinal hernias was 34.8 years.

TABLE 3.—*Sex*

Sex	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
Male	2,184	88.7	1,463	110	7.5
Female	278	11.3	205	10	4.9
Totals	2,462	100.0	1,668	120	7.2

TABLE 4.—*Race*

Race	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
White	2,298	93.4	1,560	114	7.3
Black	161	6.5	107	6	5.6
Yellow	3	0.1	1	0	0.0
Totals	2,462	100.0	1,668	120	7.2

examined immediately before a certain specific trauma considered to be the cause of a hernia, it is impossible to tell in any individual case whether the trauma was the actual cause of the hernia or only the cause of pain in an undiscovered preexisting hernia, with resultant discovery of that hernia. Also, the one definite trauma may have increased the size of the preexisting hernia, so that a previously unnoticeable hernia could be seen.

The figures listed in table 5 are based entirely on the history as given by the patient. It must be taken for granted that no hernia was present before the trauma occurred. Of course, a definite number of these patients had either a known or an undiscovered hernia before the trauma, but there is no possible way to eliminate them from the statistics.

TABLE 5.—*History of Definite Trauma As an Etiologic Factor* *

History of Trauma Given as Cause*	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
Absent	1,806	73.3	1,217	95	7.7
Positive	656	26.7	451	25	5.5
Totals	2,462	100.0	1,668	120	7.2

* Undoubtedly all or a major part of these hernias were present before the incidence of the trauma, which served only to call the patients' attention to the presence of the hernia. In this connection it is interesting to note that, among the 305 complete (congenital) indirect inguinal hernias studied, a history of definite trauma as the etiologic factor in the development of their hernias was given by 26 per cent of the patients who first noted their hernias after the age of 15 years (Shelley, H. J.: Complete Indirect Inguinal Hernias: A Study of 305 Hernias and Repairs, South. Surgeon **9**: 257-268 [April] 1940).

Slightly over one fourth of the patients, 26.7 per cent, gave a history of a definite trauma as the cause of the development of their hernias. The difference in recurrence rates, 7.7 per cent as contrasted to 5.5 per cent, was almost identical with that occurring between the white and the Negro races, possibly for much the same reason. The patients who gave a history of trauma as the cause of their hernias were on the average more muscular than those who did not give such a history. Also, one would expect to find poorer tissues to work with (again, on the average) among patients in whom a hernia developed without definite trauma than among those in whom a definite trauma was required to cause the hernia. Another factor was that hernias definitely caused by trauma are much oftener operated on sooner than those not falling within this classification, and they were on the average smaller.

SYMPTOMS

Pain.—Pain as a symptom associated with incomplete indirect inguinal hernias was noted in 49.7 per cent of the cases studied and was denied or not mentioned in 50.3 per cent.

Except for pain, as has been noted, the hernias were the cause of symptoms in practically none of the patients unless incarceration or strangulation was present. A visible bulge over the external ring or in the scrotum was noted in 73.3 per cent of the patients.

Duration.—The duration of the hernias in this group of patients as listed in table 7 was the interval between discovery of the hernia and surgical repair of the hernia or admission of the patient to the hospital.

TABLE 6.—*Pain Associated with Hernias*

History of Pain	Total Hernias	Per Cent of Entire Group
Absent	1,238	50.3
Positive	1,224	49.7
Totals	2,462	100.0

TABLE 7.—*Duration (Time Hernia was First Noted to Time of Admission or Operation)*

Duration	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
To 1 week	220	9.0	139	10	7.2
To 1 month	539	21.8	351	25	7.1
First 6 months	1,041	42.3	696	41	5.9
Second 6 months	324	13.1	229	21	9.1
To 1 year	1,365	55.4	925	62	6.7
0 to 10 years	2,136	86.6	1,446	95	6.6
10 to 20 years	217	8.8	146	16	11.0
20 to 30 years	71	2.9	51	5	9.8
30 to 40 years	24	1.0	16	1	6.3
40 to 50 years	11	0.4	7	2	28.6
50 to 60 years	2	0.08	2	1	50.0
60 to 70 years	1	0.04	0	...	...
Totals	2,462	100.0	1,638	120	7.2

The average duration (i. e., the time from which the hernia was first noted to admission or operation) of the 2,462 indirect inguinal hernias was 3.9 years.

This is not the exact figure for actual duration of the hernia in every case, but it is the closest possible approximation. Many of the hernias were undoubtedly present for a considerable period before they were first discovered.

The greatest incidence, considering the period covered, was in the duration of up to one week, 9 per cent. Likewise, the greatest incidence for any duration ending in any one month was found in the first month, 21.8 per cent. The same held true for the first six months, 42.3 per cent, and for the first year, 55.4 per cent. Only 13.1 per cent of the hernias had been noted for periods ranging from six months to one year.

A great majority, 86.6 per cent, had been present for ten years or less. Only 8.8 per cent had a duration of ten to twenty years, and the rates in the succeeding ten year periods were negligible. The average duration was three and nine-tenths years.

Recurrences.—For the hernias of this type with a duration of up to one month the incidence of recurrences was the same as the average for the entire group studied; 7.2 per cent, up to one week; and 7.1 per cent, up to one month. Hernias with a duration of up to six months showed a lower incidence of recurrences, 5.9 per cent. The rate for the second six month period was one third greater, 9.1 per cent. For the first one year period it was slightly less than the average, being 6.7 per cent.

With the exception of the fourth ten year period, which presented a recurrence rate of only 6.3 per cent, the recurrence rate tended to increase with an increase in the time the hernia had been noted preoperatively. The last four ten year periods listed contain too few followed repairs to yield accurate figures for the respective recurrence rates.

PHYSICAL FINDINGS

In a consideration of the physical factors which are of importance in estimation of the probability of the permanence of surgical cure of an incomplete indirect inguinal hernia, a number of these factors, and factors which are of primary importance, cannot be tabulated and used in the calculations. The thickness, strength and position of the various structures making up the internal ring, the walls of the inguinal canal and the external ring fall within this category, as do the various factors determining the individual patient's healing power, the strength of the resultant scar tissue and the strain which may be thrown on the inguinal region subsequent to the repair, particularly by a change of occupation on the patient's part or by unexpected and unusual trauma.

Size.—In classifying incomplete indirect inguinal hernias as to size, an arbitrary classification must necessarily be chosen. The one described later in this section was considered to be the only one into which these hernias could be definitely classified as to size. It has two major weaknesses as a measure of the condition in relation to the probability of recurrence. In the first place, it does not give an accurate indication of the diameter of the weakened area through which the hernia protrudes, and in the second place, there is a considerable variation in size within each group listed.

These hernias were divided according to size into three groups. Under size I were listed all hernias in which the sac lay entirely within the inguinal canal. Under size II were placed those in which the sac protruded from the external inguinal ring but did not extend into the scrotum. Under size III were classified those in which the sac extended into the scrotum.

The smallest number fell within size I (26.7 per cent); the greatest number, size II (40.7 per cent), and the remainder (32.6 per cent), size III (table 8).

Recurrences.—Recurrences occurred about equally with sizes I and II (6.2 and 5.7 per cent respectively), with a 50 per cent increase in size III, the figure being 9.8 per cent.

Mortality.—The mortality figures for sizes I and II were 0.27 and 0.18 per cent, and the deaths occurred in patients without either strangulation or incarceration. With size III the mortality was 1.08 per cent, but of the 5 deaths making up this figure 1 occurred in a case of incarcerated hernia and 2 in cases of strangulated hernia. The mortality figure for this group, not including the 2 deaths due to strangulation of the hernias, was 0.65 per cent, which, although small, is still three times the average mortality rate for sizes I and II (0.22 per cent).

TABLE 8.—*Size*

Size of Hernia*	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Size I	657	26.7	437	27	6.2	1 in 366 operations	0.27
Size II	1,003	40.7	682	39	5.7	1 in 544 operations	0.18
Size III	802	32.6	549	54	9.8	5 in 464 operations	1.08
Totals	2,462	100.0	1,668	120	7.2	7 in 1,374 operations	0.51

* Size I: Hernias in which the sac was limited to the inguinal canal.
Size II: Hernias in which the sac extended beyond the external ring but not into the scrotum.
Size III: Hernias in which the sac extended into the scrotum.

(Mortality rates were calculated only from the operations performed in the ten year period from 1926 to 1935).

BILATERAL HERNIAS

The subject of bilateral inguinal hernias is always of interest because of the increased possibility of recurrence when this condition is present and also because of the necessity of making a decision as to the advisability of performing the two repairs at one or at two operations.

In a consideration of this subject, those incomplete indirect inguinal hernias which occurred on one side when there was or had been an inguinal hernia of any type on the other side were classified as bilateral hernias. This could be done, as each hernia was considered individually in making up these figures. Also included under bilateral incomplete indirect inguinal hernias were those which occurred in patients who at one time had had a single incomplete indirect inguinal hernia repaired and then, later, an inguinal hernia of any type on the opposite side.

Incidence.—Of the 2,462 incomplete indirect inguinal hernias studied, only 32.7 per cent were bilateral, 67.3 per cent being unilateral. The latter figure is made up of the figures 38.7 per cent for the right side and 28.6 per cent for the left; i. e., 57 per cent of the unilateral hernias were found on the right and 43 per cent on the left. Of the total number of hernias studied in this group, 55 per cent were on the right side and 45 per cent on the left.

Recurrences.—The recurrence rate for all bilateral incomplete indirect inguinal hernias was 50 per cent greater than for unilateral hernias, the figures being 9.0 and 6.3 per cent respectively. Comparison of the recurrence rates for the two sides showed figures essentially the same for

TABLE 9.—*Unilateral and Bilateral Hernias* *

	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
Unilateral right	953	38.7	637	38	6.0
Unilateral left	706	28.6	473	32	6.8
Total unilateral	1,659	67.3	1,110	70	6.3
Total bilateral	803	32.7	558	50	9.0
Total right	1,354	55.0	917	64	7.0
Total left	1,108	45.0	751	56	7.5
Totals	2,462	100.0	1,668	120	7.2

* All hernias were counted individually. Each incomplete indirect inguinal hernia was considered one of two bilateral hernias when there was or had been an inguinal hernia of any type on the opposite side.

(A) Bilateral, repaired separately: recurrences, 9.0% (on the right, 57.7%; on the left, 42.3%).

(B) Bilateral, repaired at one operation: recurrences, 8.2% (on the right, 45.8%; on the left, 54.2%).

(C) Recurrences in bilateral hernias, 50 (right, 52%; left, 48%). Recurrences in unilateral hernias, 70 (right, 54%; left, 46%).

unilateral and bilateral hernias. The figures were: unilateral, right 6 per cent, left 6.8 per cent; total, right 7 per cent, left 7.5 per cent. What little difference there was favored the right side in both instances.

Bilateral Operations.—A great deal of discussion has been held as to the advisability of performing operations for the cure of bilateral hernias of this type in one or in two stages. In a very large proportion of this group of cases, the decision as to whether the operations should be done at one or two operations was determined rather by the nature of the hernias and the difficulties encountered in doing a satisfactory repair than by the single fact that they were bilateral. That this was a logical point in making the decision is indicated by the fact that the recurrence rate was only slightly higher for bilateral hernias repaired by two operations than for those which were repaired at one time. The logical conclusion is that the recurrence rate would have been even higher for bilateral hernias repaired at two operations had they been repaired

at the same time, although this conclusion cannot be proved from the figures. That there is no greater difference in these two recurrence rates, even though the larger hernias and those with poorer tissues were included in the group done at two operations, gives sufficient grounds to draw such a conclusion.

INCARCERATION AND STRANGULATION

Incidence.—These two complications were found in 7.8 per cent of patients with incomplete indirect inguinal hernia studied. Incarceration was present in 6 per cent and strangulation in 1.8 per cent.

Recurrences.—In the absence of both of these complications the recurrence rate among patients followed for nine months or longer was 6.9 per cent. As compared to this figure, it was 9.8 per cent in the presence of incarceration and 13.3 per cent with strangulation.

TABLE 10.—*Incarceration and Strangulation*

Strangulated or Incarcerated	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Neither	2,286	92.8	1,541	106	6.9	4 in 1,279 operations	0.31
Incarcerated*	147	6.0	102	10	9.8	2 in 81 operations	2.5
Strangulated*	44	1.8	30	4	13.2	1 in 28 operations	3.6
Totals	2,462	100.0	1,668	120	7.2	7 in 1,374 operations	0.51

* Strangulation developed in 15 old incarcerated hernias.

Mortality.—In 1,279 operations for repair of incomplete indirect inguinal hernias with which neither incarceration nor strangulation was present, the operative mortality was 0.31 per cent. In the presence of incarceration this figure was increased to 2.5 per cent, and in the presence of strangulation, to 3.6 per cent. That there is not more difference between these two figures is probably due to two factors: first, that the incarcerated hernias included a large proportion in which the sac was very large with many adherent structures in the contents, and, second, that in a considerable part of the strangulated hernias the strangulation fortunately had been present for a relatively short time. Also, strangulation accounted for part of the deaths of patients with incarcerated hernias.

RESULTS ACCORDING TO TYPE OF REPAIR

Major differences in technic only have been taken into account in the classification of these operations. Six types of repair were considered to differentiate the major variations as to operative technic, and these in turn have been subdivided according to the suture used—catgut alone or a fascial suture plus catgut.

The different types of repair were as follows:

Type 1.—Repair without transplantation of the cord, with catgut sutures only.

Type 1A.—Same as type 1 except that the conjoined tendon was sutured to the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle after the technic of McArthur.

Type 2.—Repair with transplantation of the cord between the conjoined tendon and the aponeurosis of the external oblique muscle, after the technic of Bassini, with catgut sutures only.

Type 2A.—Same as type 2 except that the conjoined tendon was sutured to the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle, after the technic of McArthur.

Type 2B.—Same as type 2 except that a fascial suture from the fascia lata was used to suture the conjoined tendon to the inguinal ligament after the technic of Gallie.

Type 3.—Repair with transplantation of the cord between the overlapped layers of the external oblique aponeurosis after the technic of Willys-Andrews, with catgut sutures only.

Type 3A.—Same as type 3, with a suture from the aponeurosis of the external oblique muscle used to suture the conjoined tendon to the inguinal ligament after the technic of McArthur.

Type 4.—Repair with transplantation of the cord external to the external oblique aponeurosis, with or without overlapping of the aponeurosis after the technic of Halsted, with use of catgut suture material only.

Type 4A.—Same as type 4, with a fascial suture from the aponeurosis of the external oblique muscle used to suture the conjoined tendon to the inguinal ligament after the technic of McArthur.

Type 5.—Any of the aforementioned types of repair in which the rectus muscle or the anterior rectus sheath was sutured to the inguinal ligament. This included no repairs in which fascial sutures were utilized.

Type 6.—Intra-abdominal excision of the sac without repair of the inguinal rings or the inguinal canal.

In a consideration of the results obtained with these various types of repair, one must bear in mind that the majority of those hernias which presented particular difficulties as to obtaining a permanent cure fell in the classifications which included either a fascial suture or a transplantation of the rectus muscle or sheath. Also, the majority of those hernias which presented the greatest probability of obtaining a permanent cure were repaired with a technic in which the cord was not transplanted.

For the reasons just stated, it is not surprising that the lowest incidence of recurrences, 4.8 per cent, was found with type 1. Neither is it surprising that in this same group was found a very low incidence of infected wounds, 0.6 per cent, as it is the simplest type of operation, requiring the least manipulation and the least ligature and suture material. The number of operations of this type in which a fascial suture was used was too small for the results to have any significance.

TABLE 11.—*Classification by Type of Repair*

Type of Repair*	Total Followed	Per Cent Recurrences	Per Cent Infections†	Per Cent Infections Showing Recurrences†	Recurrences	
					Indirect	Direct
1	163	4.8	0.6	100.0	62.5	37.5
1A	3	0.0	0.0	....	....	....
2	972	6.8	2.3	9.1	41.0	59.0
2A	197	7.8	4.7	22.2	8.7	81.3
2B	2	50.0	0.0	....	0.0	100.0
3	37	8.1	5.4	0.0	100.0	0.0
3A	1	0.0	0.0	....	....	....
4	179	9.2	4.0	14.3	35.7	64.3
4A	71	4.2	5.6	25.0	66.7	33.3
5	40	17.5	10.0	75.0	28.6	71.4
6	3	33.3	0.0	....	100.0	0.0
All repairs without fascial sutures	1,394	7.4	3.1	....	44.2	55.8
All repairs with fascial sutures	274	6.9	4.7	....	26.3	73.7
Totals	1,663	7.2	3.5	21.3	40.0	60.0

* Type 1: Repairs without transplantation of the cord.
Type 1A: Repairs without transplantation of the cord. The conjoined tendon and inguinal ligament were sutured with a fascial suture from the aponeurosis of the external oblique muscle.
Type 2: Repairs with transplantation of the cord between the conjoined tendon and the aponeurosis of the external oblique muscle.
Type 2B: Same as type 2, with suture of the conjoined tendon and the inguinal ligament with a fascial suture obtained from the fascia lata.
Type 3: Repairs with transplantation of the cord between the overlapped layers of the aponeurosis of the external oblique muscle.
Type 3A: Same as type 3, with suture of the conjoined tendon to the inguinal ligament with a fascial suture from the aponeurosis of the external oblique muscle.
Type 4: Repairs with transplantation of the cord external to the aponeurosis of the external oblique muscle, with or without overlapping of the aponeurosis.
Type 4A: Same as type 4, with suture of the conjoined tendon to the inguinal ligament with a fascial suture from the aponeurosis of the external oblique muscle.
Type 5: Repairs in which the rectus muscle or anterior rectus sheath were sutured to the inguinal ligament.
Type 6: Repairs which consisted solely of the intra-abdominal excision of the sac at the time of some other abdominal operation.
† The percentages of infections were calculated on the entire number of repairs in each group. The percentages of infected wounds showing recurrences were calculated according to the number of recurrences found among the total infected wounds which were examined in the follow-up of each group.

The majority of these incomplete indirect inguinal hernias were repaired with the technic in which the cord was transplanted between the conjoined tendon and the external oblique aponeurosis (type 2). This is the typical Bassini repair. Various refinements were added in a number of cases, such as (1) careful imbrication and suture of the transversalis fascia from the pubic spine to the point of exit of the cord from the abdomen; (2) various methods of decreasing the diameter of the cord at its point of emergence from the abdomen, and (3) overlapping of the external oblique aponeurosis superficial to the cord.

Included in this group (type 2) are the general run of hernias, from which have been removed a considerable percentage of those presenting the least and greatest difficulties in obtaining a satisfactory repair. With this type of repair the incidence of recurrences, 6.8 per cent, was slightly below the average for the entire group of incomplete indirect inguinal hernias, 7.2 per cent, and, also, the incidence of infected wounds, 2.3 per cent, was less than the average for the entire group, 3.5 per cent. Postoperative infections in the incision apparently presented a smaller hazard as to the probability of recurrence than was found with most of the other types of repairs. Only 9.1 per cent of the infected wounds were found later to show recurrences.

When a fascial suture obtained from the external oblique aponeurosis was used to suture the conjoined tendon to the inguinal ligament after the technic of McArthur in this type of repair, the recurrence rate was only 7.8 per cent. This is but slightly above that found without its use. Included in this group of repairs were a great proportion of those hernias which presented major difficulties as to obtaining a satisfactory repair. It is not unexpected that this type of repair should show both an increased percentage of infected wounds, 4.7 per cent, and an increased recurrence rate in those repairs which were infected, 22.2 per cent. The number in which a suture from the fascia lata was utilized was too small to present evidence for or against the use of this technic.

In those repairs (type 3) in which the cord was transplanted between the layers of the overlapped external oblique aponeurosis after the Willys-Andrews technic, the number of patients followed was too small to yield conclusive figures. In the small group, however, both the recurrence rate, 8.1 per cent, and the proportion of infected wounds, 5.4 per cent, were greater than the corresponding figures for the Bassini type of repair. In only 1 followed case was this type of repair performed with the use of a fascial suture from the external oblique aponeurosis to unite the conjoined tendon to the inguinal ligament.

The group in which the cord was transplanted superficial to the external oblique aponeurosis (type 4) included a somewhat greater percentage of difficult repairs than did the Bassini group. Whether or not this factor was of sufficient importance to account for an increase of one third in the recurrence rate, 9.2 per cent as compared to 6.8 per cent, there is no way of proving from the information available in the various patients' charts. The difference is great enough to suggest that the Bassini type of repair gives somewhat better results.

The incidence of infected wounds, 4 per cent, and the incidence of recurrence, 14.3 per cent, after infection were both greater than the corresponding figures for the Bassini type of repair.

When the McArthur technic was added to this type of operation the recurrence rate, 4.2 per cent, became less than 50 per cent of that

obtained without its use and also one third less than that obtained with the Bassini type of repair. The number of patients followed was too small for these figures to be conclusive, but the data would indicate that this type of repair was satisfactory.

Although only 40 patients were followed in whom a rectus transplantation (type 5) was done, the recurrence rate of 17.5 per cent showed this to have been an unsatisfactory type of repair. The large incidence of infected wounds, 10 per cent, and recurrences in 75 per cent of these infected incisions, would cause one to arrive at the same conclusion.

Intra-abdominal excision of the sac (type 6) was performed in three instances in the course of some other abdominal operation. In none of these was any attempt made to repair the inguinal canal. It is interesting to note that but 1 patient showed a recurrence in the period covered by the follow-up examinations.

The group containing all repairs in which a fascial suture was utilized was made up largely of those hernias which presented particular difficulties in obtaining a satisfactory repair. Consequently, it is most interesting that the recurrence rate, 6.9 per cent, should be the same as that observed with the Bassini type of repair, in which group a materially smaller percentage of difficult repairs was included. The incidence of infected wounds, 4.7 per cent, was twice that found in the group treated with the Bassini type of repair.

For the entire group followed, the recurrences after the repair of incomplete indirect inguinal hernias were: indirect, 40 per cent, and direct, 60 per cent. The variations from these figures according to the type of repair are interesting, but the numbers of recurrences in each group were too small to justify an appraisal of each type of repair by the fact that a majority of the recurrences were either direct or indirect.

POSTOPERATIVE COMPLICATIONS

There were 246 postoperative complications following the 2,337 repairs, or 10.4 per cent. The recurrence rate, 8.8 per cent, in these complicated cases was slightly above the average for the entire group, 7.2 per cent.

Wound infection, which developed in 3.5 per cent of the operative wounds, was the most frequent complication (unless all respiratory complications were grouped together) and acute bronchitis the next in frequency, with an incidence of 3.2 per cent. Pneumonia, if lobar pneumonia and bronchopneumonia are grouped together, was next, with an incidence of 1.8 per cent. Pulmonary atelectasis had an incidence of 0.56 per cent and a mortality rate of 7.6 per cent. The various other (less common) complications are listed in table 12.

Respiratory complications (table 13) developed after 7.3 per cent of the operations. Of these, acute bronchitis occurred with the greatest

TABLE 12.—*Postoperative Complications*

	Average Postoperative Stay in	Number Followed	Number of	Per Cent	Per Cent

TABLE 12.—*Postoperative Complications*

Complication	Total Hernias	Per Cent of Entire Group	Average Postoperative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1. Wound infection	82	3.5	21.2	57	12	21.3	....	0	0.0
2. Acute bronchitis	75	3.2	15.4	51	4	7.8	4.0	0	0.0
3. Hematomas	46	2.0	18.0	43	3	6.9	4.3	0	0.0
4. Common cold	22	0.94	16.0	8	0	0.0	0.0	0	0.0
5. Bronchopneumonia	21	0.90	18.7	13	1	7.7	9.5	1	4.76
6. Lobar pneumonia	18	0.77	22.4	12	3	25.0	11.1	2	11.1
7. Pulmonary atelectasis	13	0.56	19.5	9	1	11.1	0.0	1	7.6
A. Atelectasis (right lung)	9	0.38	19.2	7	0	0.0	0.0	1	11.1
B. Atelectasis (lower lobe of right lung)	3	0.13	20.5	2	1	50.0	0.0	0	0.0
C. Atelectasis (left lung)	1	0.04	18.0	0	..	....	0.0	0	0.0
8. Pulmonary embolus	9	0.38	24.4	4	1	25.0	0.0	1	11.1
9. Deep phlebitis	7	0.30	33.0	6	0	0.0	0.0	0	0.0
10. Pyelitis	6	0.26	20.0	6	1	16.7	16.7	0	0.0
11. Acute tonsillitis	3	0.13	12.7	3	0	0.0	0.0	0	0.0
12. Cystitis	3	0.13	18.0	2	0	0.0	0.0	0	0.0
13. Acute otitis media	3	0.13	24.3	3	0	0.0	0.0	0	0.0
14. Pleurisy with effusion	3	0.13	29.0	2	0	0.0	33.3	0	0.0
15. Epididymitis	3	0.13	19.3	3	1	33.3	0.0	0	0.0
16. Conjunctivitis	2	0.09	13.5	2	0	0.0	0.0	0	0.0
17. Delirium tremens	2	0.09	14.0	0	..	....	0.0	1	50.0
18. Myocardial failure	2	0.09	8.1	0	..	....	0.0	2	100.0
19. Chickenpox	1	0.04	11.0	1	0	0.0	0.0	0	0.0
20. Measles	1	0.04	10.0	1	0	0.0	0.0	0	0.0
21. Mumps	1	0.04	15.0	0	..	....	0.0	0	0.0
22. Prostatic abscess	1	0.04	58.0	1	1	100.0	100.0	0	0.0
23. Empyema	1	0.04	103.0	1	0	0.0	0.0	0	0.0
24. Psychoneurosis	1	0.04	22.0	1	0	0.0	0.0	0	0.0
25. Anxiety state	1	0.04	20.0	1	0	0.0	0.0	0	0.0
26. Toxic psychosis	1	0.04	46.0	1	0	0.0	0.0	0	0.0
27. Renal calculus (passed)	1	0.04	15.0	0	..	....	0.0	0	0.0
28. Uremia	1	0.04	46.0	1	0	0.0	0.0	0	0.0
29. Hemorrhage (reoperated on)	1	0.04	30.0	1	0	0.0	100.0	0	0.0
30. Cerebral hemorrhage	1	0.04	1.5	0	..	....	0.0	1	100.0
31. Pericarditis	1	0.04	14.0	0	..	....	0.0	1	100.0
32. Acute glaucoma	1	0.04	14.0	1	0	0.0	0.0	0	0.0
33. Furunculosis	1	0.04	14.0	0	..	....	0.0	0	0.0
34. Peritonsillar abscess	1	0.04	15.0	1	0	0.0	0.0	0	0.0
35. Vincent's angina	1	0.04	21.0	1	0	0.0	0.0	0	0.0
36. Parietal peridontal abscess	1	0.04	12.0	0	..	....	0.0	0	0.0
37. Peripheral neuritis	1	0.04	33.0	0	..	....	0.0	0	0.0
38. Pulmonary abscess	1	0.04	45.0	0	..	....	0.0	1	100.0
39. Exacerbation of hyperthyroidism	1	0.04	33.0	0	..	....	0.0	0	0.0
Totals	246	10.4	....	170	15	8.8	5.0*	7†	2.85

* Five per cent of infected wounds occurred among the patients with postoperative complications (excluding those whose only complication was wound infection).
† Four patients who died postoperatively each had two complications.

TABLE 13.—*Postoperative Respiratory Complications*

Complication	Total Hernias	Per Cent of Entire Group	Average Postoperative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1. Acute bronchitis	75	3.2	15.4	51	4	7.8	4.0	0	0.0
2. Common cold	22	0.94	16.0	8	0	0.0	0.0	0	0.0
3. Bronchopneumonia	21	0.90	18.7	13	1	7.7	9.5	1	4.76
4. Lobar pneumonia	18	0.77	22.4	12	3	25.0	11.1	2	11.1
5. Pulmonary atelectasis	13	0.56	19.5	9	1	11.1	0.0	1	7.6
A. Atelectasis (right lung)	9	0.38	19.2	7	0	0.0	0.0	1	11.1
B. Atelectasis (lower lobe of right lung)	3	0.13	20.5	2	1	50.0	0.0	0	0.0
C. Atelectasis (left lung)	1	0.04	18.0	0	..	....	0.0	0	0.0
6. Pulmonary embolus	9	0.38	24.4	4	1	25.0	0.0	1	11.1
7. Acute tonsillitis	3	0.13	12.7	3	0	0.0	0.0	0	0.0
8. Acute otitis media	3	0.13	24.3	3	0	0.0	0.0	0	0.0
9. Pleurisy (with effusion)	3	0.13	29.0	2	0	0.0	33.3	0	0.0
10. Empyema	1	0.04	103.0	1	0	0.0	0.0	0	0.0
11. Peritonsillar abscess	1	0.04	15.0	1	0	0.0	0.0	0	0.0
12. Pulmonary abscess	1	0.04	45.0	0	..	....	0.0	1	100.0
13. Vincent's angina	1	0.04	21.0	1	0	0.0	0.0	0	0.0
Totals	171	7.3	....	108	10	9.2	4.7	5*	2.9

* One patient that died had two respiratory complications.

TABLE 14.—*Postoperative Circulatory Complications*

Complication	Total Hernias	Per Cent of Entire Group	Average Postoperative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1. Hematomas	46	2.0	18.0	43	3	6.9	4.3	0	0.0
2. Pulmonary embolus	9	0.38	24.4	4	1	25.0	0.0	1	11.1
3. Deep phlebitis	7	0.30	33.0	6	0	0.0	0.0	0	0.0
4. Myocardial failure	2	0.09	8.1	0	..	....	0.0	2	100.0
5. Hemorrhage—patient reoperated on	1	0.04	30.0	1	0	0.0	100.0	0	0.0
6. Cerebral hemorrhage	1	0.04	1.5	0	..	....	0.0	1	100.0
7. Pericarditis	1	0.04	14.0	0	..	....	0.0	1	100.0
Totals	67	2.8	....	54	4	7.4	4.5	4*	6.0

* One patient that died had two circulatory complications.

frequency, 3.2 per cent. Following that came, in order, the common cold, 0.94 per cent; bronchopneumonia, 0.90 per cent; lobar pneumonia, 0.77 per cent, and pulmonary atelectasis, 0.56 per cent.

The recurrence rate for the entire group of respiratory complications was 9.2 per cent, essentially the same as that found for the total complicated cases.

Circulatory complications developed after 2.8 per cent of the operations (table 14). Hematomas, 2 per cent, pulmonary embolus, 0.38 per cent, and deep phlebitis, 0.20 per cent, accounted for the majority of these complications. The recurrence rate of 7.4 per cent was the same as for the entire group of repairs and was less than was associated with respiratory complications.

TABLE 15.—*Deaths (1926-1935)*

Operative Deaths †	Patient's Age	Hernia Strangulated	Duration of Strangulation	Resection Required	Time of Death After Operation	Cause of Death
1	30	No	..	..	28 hours	Delirium tremens; myocardial failure
2	42	No	..	..	2 days	Bronchopneumonia; mitral stenosis
3	43	No	..	..	45 days	Atelectasis of right lung; abscess of upper lobe of right lung
4	53	No	..	..	14 days	Lobar pneumonia; pericarditis
5	56	Yes	4 days	No	15 days	Pulmonary infarct; myocardial failure
6	63	No	..	..	36 hours	Cerebral hemorrhage
7	66	Yes	4 days	No	6 days	Lobar pneumonia
Nonoperative Deaths						
1*	65	Yes	4 days	Patient moribund; too ill for operation		Intestinal obstruction

* This patient also had a hernia on the opposite side.
† Seven deaths in 1,374 operations—mortality rate, 0.51 per cent.

OPERATIVE MORTALITY

Listed in table 15 are the postoperative deaths and 1 death of a patient with a strangulated hernia who arrived at the hospital moribund and was not operated on. The mortality figures are based on the 1,374 repairs done in the ten year period 1926 to 1935 inclusive.

The total mortality was 0.51 per cent. For hernias without incarceration or strangulation the mortality rate was 0.32 per cent; in the presence of incarceration, the rate was 2.5 per cent, and with strangulation it was 3.6 per cent (table 10).

FOLLOW-UP DATA

Of the 2,462 patients studied, 125 were not operated on, and the hernias of 2,337 were repaired by operation. Of the latter, 364 did not return for follow-up examination. Among the 1,973 who did return

for follow-up examination, 120 were found to have a recurrence. The average length of follow-up time was thirty-one months for all patients followed.

However, a follow-up period of less than nine months was considered too brief, so that for purposes of study only those patients observed over a postoperative period of nine months or longer were

TABLE 16.—*Follow-up Data*

(A)

Total number of hernias studied	2,402	
Total with no operation	125	
Total operations	2,337	
Total operative deaths	7	
Total with no follow-up examination	364	
Total with follow-up under 9 months—no recurrence	305	
Total with follow-up 9 months and over (including recurrences)	1,668	
Average follow-up time—all cases followed 9 months and over	36	months
Total recurrences	120	
Average time recurrences were first noted postoperatively	32.2	months
Percentage of recurrences with follow-up of 9 months and over	7.2	
Total number of operations examined postoperatively	1,973	
Average follow-up time for all followed cases	31	months
Total recurrences	120	
Percentage of recurrences for all followed cases	6.1	

Recurrences: indirect, 40 per cent; direct, 60 per cent

(B)

Length of Follow-Up Time *	Total Operations Followed	Percentage of All Followed Operations	Total Recurrences Discovered	Percentage of Total Recurrences	Recurrence Percentage for Group
Under 9 months	340	17.5	35	29.7	10.3
9 months to 1 year	220	11.1	17	14.4	7.9
Under 1 year	560	28.6	52	44.1	9.3
1 to 2 years	495	24.9	27	22.9	5.5
2 to 3 years †	557	28.1	14	11.7	2.5
3 to 5 years ‡	107	5.3	6	5.1	5.7
5 to 10 years	150	7.5	13	11.0	9.0
10 to 15 years	67	3.4	5	4.2	7.5
15 to 22 years	37	1.9	3	2.5	7.5
Totals	1,973	100.0	120	100.0	6.1

* Cases included only when the period of follow-up time was ended by failure to return again for examination or by the discovery of a recurrence.

† One third of the recurrences were discovered 2 years or longer after the operation.

‡ Nearly one fourth of the recurrences were discovered 3 years or longer after the repair was done.

included in the figures throughout the study. This included 1,668 hernia repairs, with an average follow-up period of thirty-six months and a recurrence rate of 7.2 per cent. The average time postoperatively at which recurrences were discovered was thirty-two and two-tenths months, with the shortest time immediately after the operation and the longest time nineteen years.

Nearly one third (29.7 per cent) of the recurrences were discovered under nine months postoperatively; 44.1 per cent in the first year; 22.9 per cent in the second year; 11.7 per cent in the third year; 5.1

per cent in the fourth and fifth years; 11 per cent from the fifth to the tenth year; 4.2 per cent from the tenth to fifteenth year, and 2.5 per cent after the fifteenth year.

Of the 120 recurrences following repair of incomplete indirect inguinal hernias, 40 per cent were indirect and 60 per cent were direct.

DURATION OF POSTOPERATIVE HOSPITALIZATION

The question has often arisen as to the possibility of decreasing the incidence of recurrence following hernia repairs by increasing the duration of postoperative hospitalization. Such a procedure, if proved of value, would add little to the economic loss of wage-earning patients, as they would still return to their work in the same length of time. The added cost of hospitalization would have to be balanced against the value of the decreased liability to the development of recurrences.

Patients without complications who were kept in the hospital for more than the customary eleven to fifteen days were, in the majority of instances, patients whose hernias presented the greatest likelihood of recurrence. A certain proportion, but a much smaller one than that just under discussion, remained in the hospital for a longer period for one of the two following reasons. In the case of bilateral hernias repaired at two operations but with one admission to the hospital, the hernia repaired first automatically called for a longer postoperative hospitalization than the second repair (by between ten and fifteen days). Without taking into consideration the length of postoperative hospitalization, repair of bilateral hernias in this group was followed by a recurrence rate of 9 per cent, as compared to 6.3 per cent for unilateral hernias. The second group is made up of those cases in which bilateral repair was done at one operation and some local complication developed in one repair, necessitating an increased length of hospitalization and thereby also increasing the time of hospitalization for the uncomplicated repair.

For the results to have any value in determining the effect of increased hospitalization in decreasing the recurrence rate, the complicated cases must be eliminated.

Table 17 lists the findings in this study. The last three lines give the pertinent results. The more detailed figures in the upper part of the table are given to show that the figures in the three lower divisions are not thrown off by unfair inclusions.

The number of repairs for which the patient's were hospitalized postoperatively for less than eleven days is too small for the recurrence rate to have a comparative value. They are listed separately, as it was not considered fair to include them in the list with the ordinary length of hospitalization.

The recurrence rate for the 1,110 repairs without postoperative complications in which the patients were kept in the hospital for eleven to

sixteen days was 7 per cent. For the 334 repairs without postoperative complications in which the patients were kept in the hospital for more than fifteen days the recurrence rate was 4.5 per cent. The ordinary length of postoperative hospitalization is found to carry a recurrence expectancy 55.5 per cent greater than that noted when this period is more than fifteen days. This is particularly noteworthy when one considers that this group of repairs is made up largely of hernias with which otherwise an increased incidence of recurrence would have been expected.

CONCLUSIONS AND COMMENT

1. From this study it is apparent that, to aid in keeping the recurrence rate low after operative repair of incomplete indirect inguinal

TABLE 17.—*Time Patients Were Kept in the Hospital After Operative Repair*

Postoperative Time in Hospital, Days	Total Operations			Without Postoperative Complications			With Postoperative Complications		
	Number Followed	Recurrences	Per Cent Recurrences	Number Followed	Recurrences	Per Cent Recurrences	Number Followed	Recurrences	Per Cent Recurrences
2 to 11.....	13	1	7.7	12	1	8.4	1	0	0.0
11 to 13.....	99	7	7.1	96	6	6.3	3	1	33.3
13.....	265	14	5.3	247	13	5.3	18	1	5.6*
14.....	580	41	7.1	538	40	7.4	42	1	2.4*
15.....	247	20	8.1	229	19	8.3	18	1	5.6*
16 to 22.....	386	30	7.8	306	14	4.6	80	16	20.0
22 and over.. (over 3 weeks)	78	7	9.0	28	1	3.6	50	6	12.0
Under 11.....	13	1	7.7	12	1	8.4	1	0	0.0
11 to 16.....	1,191	82	7.0	1,110	78	7.0	81	4	5.0*
More than 15	464	37	8.0	334	15	4.5	130	22	16.9
Totals...	1,668	120	7.2	1,456	94	6.6	212	26	12.3

* These patients were mostly children and the complications chiefly minor.

hernias, the operations should be performed soon after the appearance of the hernia. This is borne out by the figures showing an absence of recurrence in the first fifteen years of life and by a very low figure for the next ten years of life, with an increasing rate for the greater ages (tables 1, 2 and 7). Also, when the hernia was permitted to remain sufficiently long for it to become scrotal, the incidence of recurrences increased by 50 per cent, and the mortality rate became five times greater than when the hernias were smaller.

2. The question as to whether bilateral hernias should be repaired at one operation or two cannot be answered conclusively by the figures shown in table 9. Since the recurrence rate for operations done in two stages was only slightly greater than that for those done at one stage, the conclusion is probably justified that the larger and more difficult bilateral hernias should be repaired in two operations. This statement is made because in the cases studied this was largely done. Only a

slight increase in the recurrence rate was found, although the majority of hernias operated on in two stages were certainly associated with a greater expectation of recurrence than those repaired at one operation.

However, as in deciding on the length of time a patient should be kept in the hospital after the operation, the economic factor must necessarily be taken into account. The patient's ability to pay for two periods of hospitalization instead of one and to be away from work for two periods instead of one should probably be the determining factor unless both hernias present unusual obstacles to the performance of a satisfactory repair. In this case the repairs should be performed at two operations, preferably with two separate admissions to the hospital.

For those bilateral hernias which must of necessity be repaired at one operation, an extended stay in bed will to a certain degree limit the expected increase in the recurrence rate.

3. Both incarceration and strangulation increase the expectation of recurrence by 30 to 100 per cent and give mortality rates eight and eleven times greater respectively. It is obvious that incomplete indirect inguinal hernias should be operated on early, before either of these complications develops.

4. Meticulous care should be used in the performance of the operation to prevent wound infection and hematomas, particularly since the former gives a recurrence rate three times the average for the entire group (table 12).

Pulmonary and circulatory complications can be kept at a minimum by careful administration of a properly selected anesthetic, maintenance of passive and active motion of the patient's muscles and frequent changes of the patient's position in bed postoperatively. Rigid refusal to operate on patients having even the slightest evidence of a common cold will aid materially in the reduction of respiratory complications. These points are all very important, as both the mortality rate and the recurrence rate are increased by respiratory complications, and circulatory complications increase mortality (tables 13 and 14).

5. The type of repair must be chosen for each individual hernia. There are so many factors involved that, because in a set of figures such as those given in table 11 one type of operation results in a low recurrence rate, it would be irrational to conclude that this type of repair should be applied to all hernias.

(*a*) These figures justify the statement that adding suture of the rectus muscle or of the anterior sheath of the rectus muscle to any type of repair of an incomplete indirect inguinal hernia is not a satisfactory procedure.

(*b*) Probably transplantation of the cord external to the external oblique aponeurosis does not give as satisfactory results as does the

Bassini type of transplantation. However, the possible inclusion of a greater percentage of difficult repairs in this group may have accounted for the increase in the recurrence rate of nearly 50 per cent.

(*c*) The figures obtained would indicate that the Willys-Andrews type of repair is an unnecessary addition to the required operative manipulation, although the number of cases in this group was too small to give definite proof.

(*d*) For the larger hernias, for those in patients with poor structures and when there is a definite direct weakness, the figures indicate definitely that the use of a fascial suture after the technic of McArthur gives a slightly lower recurrence rate than that observed without its use in a group of hernias in which supposedly a lower recurrence rate is more readily obtained.

6. In all cases in which the patient's financial circumstances permit, hospitalization for a minimum of sixteen days will be repaid by a decrease in the expected rate of recurrence. With hernias which are large or bilateral or which present other factors increasing the expectancy of recurrence, a minimum period of three weeks' hospitalization should be provided for.

REPAIR OF INCOMPLETE INDIRECT INGUINAL HERNIAS

The opinions about to be expressed are the result of the findings in this study and observations made in my own experience, combined with those points I have been able to glean from the opinions of other surgeons with more extensive experience in this type of surgical practice.

The first and most important point is that each hernia and each patient must be considered individually. The many possible combinations of the many factors involved make it impossible to outline one method of treating all hernias of this type or even a few set plans to cover this type of hernias as divided into a few broadly inclusive groups.

A few general points in the technic must be applied to all operations. Among these are careful preparation of the skin; refusal to proceed with the operation when the skin is macerated or roughened or presents any evidence of infection; clean, careful dissection with the least possible trauma to the tissues; inclusion of the least possible tissue in the clamps and ligatures when bleeding vessels are grasped; careful and complete hemostasis, so obtained that later bleeding is impossible; tying of all sutures with only sufficient tension to obtain approximation, and careful closure of the entire wound so that no dead spaces remain (and this includes avoidance of closing the wound when the edges of the skin are raised, thereby leaving air enclosed in the wound).

I am convinced from my own experience and by the figures cited by various authors that the use of fine silk for suture and ligature material throughout the operation is a valuable addition to the technic

of hernia repair. This gives a wound that heals cleanly, without reaction in or about it. Silk of the finest size which will prove adequate should be used for ligatures and sutures. All sutures should be interrupted. The knots should be carefully placed and the ends cut as short as safety will permit.

When the cord is larger than normal, it should be reduced in diameter at the point of emergence from the internal inguinal ring by incising part or all of the fibers of the cremasteric muscle. In particularly difficult closures in the region of the internal ring, a worth while procedure is separation of the vas and the vessels of the cord so that their points of exit from between the approximated conjoined tendon and inguinal ligament are separated by two or three sutures, as described by Torek.

A very important point is division of a small branch of the deep epigastric artery, which enters the cord. Its division facilitates the formation of a suitably small internal ring.

I am convinced that the formation of a smooth floor between the preperitoneal fat and the suture line uniting the conjoined tendon to the inguinal ligament will reduce the tendency to recurrence. This is obtained by placing a row of interrupted sutures from the pubic spine to the medial side of the internal ring. In the medial two thirds or three fourths of the wound this suture imbricates the loose transversalis fascia so that the inferior edge of the conjoined tendon is approximated to the shelving portion of the inguinal ligament. In the upper one third or one fourth of the inguinal canal it approximates the edges of the transversalis fascia, which were opened when the branch from the deep epigastric artery was cut. In this area, this fascia in addition is imbricated sufficiently to bring over the retracted inferior edge of the conjoined tendon as was done in the lower portion of the inguinal canal.

The interrupted sutures approximating the conjoined tendon to the inguinal ligament are placed but not tied in turn, from below upward to the site of the internal ring. The first suture is placed so that it includes the attachment of these two structures to the pubis and is introduced at right angles to their fibers. Each suture is then placed sufficiently close to the one below so that adequate and close approximation will be obtained between these two structures.

For several years I have made a practice of placing the highest suture (below and medial to the new internal ring) so that it includes only muscle above and below the point of exit of the cord. When it is tied, the entire internal ring is made up of muscle. As a result, the closure about the cord may be done firmly. Since this method has been used, no recurrences at this site and no swollen testicles have been noted.

One or two sutures may be placed above the internal ring but probably have no value in the ultimate outcome of the repair unless, in the operative procedure, the attachment of the internal oblique muscle and inguinal ligament was separated above the internal ring.

These sutures are then tied with only sufficient tension to approximate the conjoined tendon to the inguinal ligament.

A new external ring is formed by approximating the edges of the external oblique aponeurosis at a point below where this aponeurosis was originally incised. This point is chosen to make the size of the external ring such that it will admit the tip of the operator's little finger beside the cord. Before this first suture is tied, the cord is pulled downward until it lies in a straight line in the new inguinal canal. The remaining edges of the external oblique aponeurosis are then approximated by interrupted sutures from below upward. I have used this method of closure for several years, because it facilitates greatly the formation of the new external ring and closure of the external oblique aponeurosis.

The subcutaneous tissue is approximated by the use of interrupted sutures which include only a small bit of the cut deep fascia on each side of the incision. The skin may be closed by whatever technic the individual operator prefers, but Michel clips have given the most satisfactory scars in my experience.

As to variations from the technic which has just been described, in order to fit the needs of the different individual repairs a wide experience is of the greatest value, provided the surgeon has faced the various problems with an open mind and observed carefully the results obtained in the several manipulations with which attempts have been made to meet those problems.

Undoubtedly, if repairs without transplantation of the cord are to be done, they should be reserved for the repair of hernia in young children, in whom the internal ring is small preoperatively, the muscular and fascial structures are well developed and strong and no weakness of the posterior wall of the inguinal canal is present.

Whether or not transplantation of the cord external to the external oblique aponeurosis is a worth while procedure is at least a questionable point. It causes loss of the normal obliquity of the inguinal canal and prevents to a large degree the normal action of the abdominal muscles in protecting the inguinal area from the results of forces applied from within the abdomen. The figures in this study would at least suggest that it is a procedure which does not give added support to the repair and possibly results in a weaker inguinal region. I believe definitely that the formation of a new inguinal canal external to one of two flaps of an overlapped external oblique aponeurosis results in a weaker repair than does the Bassini repair.

In the experience at St. Luke's Hospital, the use of fascial sutures in the more difficult repairs of incomplete indirect inguinal hernias appears to be a worth while procedure. Great care in the proper insertion and anchoring of this type of suture is important. Maintenance of asepsis, care in handling of tissues, hemostasis, avoidance of tension on the sutures, particular care not to damage the inguinal ligament and staggering of the successive point of entrance of the suture into and points of exit from the inguinal ligament are necessary if satisfactory results are to be obtained. I feel that it is very important to anchor each successive suture both to the conjoined tendon and to the inguinal ligament with a fine silk suture. Each fixation suture should include, in turn, a bit of the structure through which the fascial suture passes, the entire thickness of the fascial suture and again, on the opposite side, the structure through which the fascial suture passes. This effectively closes the hole made by the needle in introducing the fascial sutures at the same time that the suture is anchored.

If this fascial suture is to extend above the internal ring, it should pass the point of exit of the cord on the same side as the inguinal ligament, so that the internal ring will be made up entirely of the actual muscle of the internal oblique and transversalis muscles.

This fascial suture formed by a strip of the external oblique aponeurosis will be found satisfactory for practically all of the types of hernia under discussion. However, an occasional hernia, with an enormous internal ring with poor internal oblique and transversalis muscles or with a very wide weakened area in the posterior wall of the inguinal canal and inadequate muscles, may require for satisfactory repair the use of a fascial suture obtained from the fascia lata.

Various authors have advocated replacement of fascial sutures by a silk technic. This, in my experience, is satisfactory in some cases, but I feel that better results will be obtained by adding the use of a fascial suture to the silk technic in the more difficult repairs. Silk technic with and without fascial sutures has been used for too short a time at St. Luke's Hospital for figures to be available to demonstrate by follow-up results the value of this technic and to determine whether it is advisable to give up entirely the use of fascial sutures, as has been suggested by some authors.

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CEREBRAL COMPLICATIONS FOLLOWING SURGICAL OPERATIONS

II. FACTORS WHICH PREDISPOSE TO CEREBRAL ANOXIA

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In a recent article [1] we discussed the etiologic, pathogenic and pathologic aspects of the cerebral complications of surgical operation. We have included among the cerebral complications many of the spectacular "anesthetic deaths" and postoperative hemiplegias, as well as the less spectacular but equally tragic postoperative confusional states, psychoses, prolonged comas and convulsions. In all, 21 cases of fatal cerebral complications were reported, with autopsy observations in each case.

Such cerebral complications are not, however, invariably fatal. Indeed, it seems certain that many more patients recover than die, although not all recover without residual stigmas. However, in order to establish the etiologic factors in certain types of postoperative cerebral complications it was thought imperative to use only cases in which careful postmortem examinations had been made.

Thus we have been able to demonstrate that most types of postoperative cerebral complications may occur as a result of cerebral anoxia. In the cases studied by us, anoxia was usually secondary to an acute general circulatory collapse precipitated by administration of an anesthetic plus the trauma of operation in patients whose margin of circulatory reserve had been reduced. In many cases the presence of such a preexisting chronic circulatory insufficiency was unsuspected either by the patient or his physician, but histologic observations in the vital organs were interpreted as evidence of such a disturbance.

While the cerebral changes in our cases appeared to be the result of anoxia operating through general circulatory insufficiency, it was evident that such anoxia may be produced by various mechanisms and that more than one mechanism may be present in a given case. As

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1. Behrend, A., and Riggs, H. E.: Cerebral Complications Following Surgical Operation: I. Etiology and Pathology, Arch. Surg. **40**:24-42 (Jan.) 1940.

Barcroft [2] and others have stated, there are four main types of anoxia. The first is stagnant anoxia, in which, because of slowing of the blood current, tissue asphyxia occurs. The second is anemic anoxia, which occurs when the hemoglobin content of the blood is too low to allow sufficient oxygen to be carried to the tissues. The third is histotoxic anoxia, which occurs when the cells are so damaged as to be unable to utilize oxygen. A common cause of this condition is the over-enthusiastic use of morphine, barbiturates, anesthetic drugs or alcohol. The fourth is anoxic anoxia, which may occur throughout the body as a result of an insufficiency of the available supply of inspired oxygen or locally as the sequel of trauma, acute inflammation or gas gangrene. On the basis of such physiologic concepts it is evident that anoxia plays a role in many medical and surgical conditions.

ORGANIC HEART DISEASE

The integrity of the brain is dependent on the efficiency of the general circulation. The cells of the brain are the most highly differentiated of the body and not only require more oxygen than do the others but are the first to show the effects of lack of oxygen. Thus, while every organ suffers under the stress of anoxia, damage to brain cells may be irreversible, and the symptoms referable to the brain are the most spectacular. It is apparent that any pathologic process affecting the heart or the blood vessels which results in a reduction of adequate blood flow to the cerebrum may contribute to the production of cerebral complications.

It would appear, then, that cardiocirculatory disorders would themselves play an important if not an essential role in predisposing to postoperative cerebral accidents. This fact we have been able to confirm. Of the 21 patients in the cases previously reported, 76 per cent showed postmortem evidence of an organic cardiocirculatory lesion existing prior to operation. It is important to emphasize that the degree of cardiac decompensation need not be severe. Nevertheless, any situation which impairs the integrity of the myocardium and the vascular system may produce a mild state of chronic tissue asphyxia. Owing to the adaptability of the organism such conditions may produce no clinical sign under ideal conditions. But when an organism so damaged is subjected to the stress of an added acute anoxia, its ability to withstand such stress may be impaired, and irreparable damage may result.

ANEMIAS

Severe anemias, either acute (hemorrhagic) or chronic, predispose to cerebral accidents. Yet it frequently becomes necessary to operate

2. Barcroft, J.: Anoxaemia, Lancet **2**:485-489 (Sept. 4) 1920.

on anemic patients. The added risks of operation in such cases can hardly be overemphasized. Chronic anemias in time produce myocardial damage. Under such circumstances, the ability of the heart to supply a sufficient blood flow to the cerebrum must be impaired. In addition, the amount of hemoglobin available to carry oxygen to the brain is materially reduced. In these circumstances the brain suffers a chronic depletion in the normally high amount of oxygen required to carry on its vital functions. While in ordinary circumstances no clinical evidence of resultant damage is apparent, chronic degenerative changes are commonly observed in the brain at postmortem examination. Under conditions requiring operation, when the blood pressure is frequently lowered, when additional blood is lost and when an anesthetic is administered which may further deplete the oxygen content of the blood, the acute changes superimposed on the preexisting chronic damage may be sufficient to cause cellular injury.

Recently our attention was called to the case of a young woman who was brought to a hospital in another city, having suffered severe loss of blood as a result of an incomplete abortion. Shortly after her admission to the hospital, curettement was performed with the patient under nitrogen monoxide and oxygen anesthesia. When the mask was removed the patient had a convulsion, and artificial respiration had to be instituted. After six weeks of vegetative existence she died of terminal bronchopneumonia. Nothing grossly abnormal was observed on examination of the brain and viscera except the aforementioned pneumonia. Microscopic examination of the brain might have revealed areas of cellular degeneration.

The dangers inherent in operating on patients with a severe degree of anemia canont be overemphasized, and obviously the fact that the operation is of a minor nature and the anesthesia of short duration cannot minimize the danger. In a brain already suffering from relative chronic anoxia the added stress of a period of acute anoxia can produce irremediable damage, such as that which apparently occurred in the case just cited.

ANATOMIC FACTORS

It seems highly probable as a result of our studies that anatomic factors can influence the quantitative supply of blood to the brain and so play an important part in the production of postoperative cerebral accidents. It may be of interest to recall the work of Donaldson,[3] who

3. Donaldson, H. H., and Canavan, M. M.: A Study of the Brains of Three Scholars, J. Comp. Neurol. **46**:1-95 (Aug.) 1928. Donaldson, H. H.: The Brain Problem—in Relation to Weight and Form, Am. J. Psychiat. **12**:197-214 (Sept.) 1932.

carried out most careful postmortem studies on the brains of Sir William Osler and several other scholars and compared them with those of a group of ordinary hospital patients. After intensive study, Donaldson was forced to conclude that the only feature which distinguished genius from mediocrity anatomically was the greater vascularity of the brains in the former group.

As Riggs and Griffiths [4] have shown, individual variations in the pattern of the vessels which arise from the circle of Willis to supply the two halves of the cerebrum are extremely common. This may help to explain why in some cases of diffuse cerebral cellular damage in our series the clinical symptoms were referred to only one side of the brain, as was evidenced by hemiplegia. Frequently in such cases there are anomalies of the blood vesesls supplying the affected side. In other words, on the side with the poorer blood supply the degree of cellular damage is greater.

AGE

It might be supposed that cerebral complications are most to be feared in older patients. Elderly patients with arteriosclerosis who become psychotic after an accident or an operation are common. Impaired elasticity of the blood vessels, diminution of the vessel diameter and slowing of the blood current undoubtedly contribute to the production of these complications. Yet the majority of our patients whose death could be traced most directly to cerebral anoxia were between the ages of 20 and 50 years.

One explanation may be found in the fact that the number of operations performed is much greater in the age groups between 20 and 50 years.[5] Furthermore, it should be recalled that the basal metabolic requirements of younger persons are greater than those of persons in the older age group. Consequently, any relative lack of oxygen will be most keenly felt by the younger persons.

METABOLIC DISORDERS

Cerebral complications occurring with or without operation in cases of severe hyperthyroidism are not uncommon. Several factors may combine to produce the symptoms. "Thyroid heart" and hypertension are often present. The rate of blood flow is disturbed, and the circulation time is increased, as is the demand for oxygen. Under such circumstances, not only does the brain suffer but the liver and the heart feel the effects of oxygen want.

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4. Riggs, H. E., and Griffiths, J. O.: Relation of Anomalies of Circle of Willis to Cerebral Circulation: Preliminary Report, read at the Annual Meeting of the American Association of Neuropathologists, Atlantic City, N. J., May 2, 1938.

5. Berkson, J.: Personal communication to the authors.

Thyroid crisis is a condition much feared and little understood. It may occur with or without operative intervention on the thyroid gland, but operation is particularly likely to precipitate it. This is readily explainable because of the additional anoxic factors introduced by the operation, namely, the administration of an anesthetic, the subsequent loss of fluid and blood and the disturbances of temperature regulation which commonly follow operation. No one has ever been able to calculate the oxygen requirements of a person in thyroid crisis, but they must indeed be enormous, and the rate of tissue catabolism must be correspondingly high. When death occurs, the usual terminal picture is marked by spectacular hyperpyrexia, the temperature in many instances reaching 108 F. or more. It may be of some significance that a similar terminal hyperpyrexia is observed in some cases of so-called "liver death" following cholecystectomy, for which no really adequate explanation has ever been offered.

It has also been our experience that in cases in which cerebral complications have developed after surgical operation the terminal temperature is similarly high in most cases in which the patients do not die immediately after the operation. Possibly the three conditions just mentioned have some connection, and at present we are undertaking clinical and experimental investigations in an effort to determine whether such a connection exists. Recent work [6] which indicates that toxic polypeptides absorbed in the blood stream are the cause of the so-called hepatorenal syndrome may help to throw light on the subject. Presumably, widespread tissue anoxia can cause damage sufficient to liberate such large amounts of these toxic substances that the liver and kidneys are overwhelmed in their efforts to remove them.

SURGICAL EMERGENCIES

Among the surgical emergencies which predispose to postoperative cerebral complications are shock, hemorrhage and overwhelming infections, such as peritonitis. It may be superfluous to emphasize at this point that in every surgical emergency each organ of the body suffers. That under some conditions the brain is the most seriously damaged organ has already been noted. Undoubtedly there are cases in which the patient is in such severe shock or is so ill at the time he is seen by the surgeon that irreparable damage has already occurred before operation is contemplated. There is, of course, little that can be done for such patients, but we are concerned here not with these but with the cases in which further damage can be prevented if the mechanism of production is better understood.

6. St. Jacques, E.: The Hepatorenal Syndrome, J. Internat. Coll. Surgeons **2**:295-297 (Oct.) 1939.

According to Moon,[7] shock is a circulatory deficiency, neither cardiac nor vasomotor in origin, characterized by decreased blood volume, by decreased cardiac output (reduced volume flow) and by increased concentration of the blood. But it matters little to which of the theories of shock one subscribes. Whatever the mechanism may be, and it doubtless varies in different cases, the result is tissue anoxia. This anoxia is probably the most important factor tending to increase or perpetuate the circulatory deficiency.

Shock is always accompanied by a fall in venous pressure, and it has frequently been noticed that the fall in venous pressure precedes the fall in arterial pressure. Weiss and his associates[8] have been able to show that the peripheral collapse induced by the administration of sodium nitrite with the patient in the upright position can produce a state of shock independent of any cardiac or peripheral arterial failure. The clinical importance of the venous side of the circulatory system has probably not received its just share of attention.

ANESTHESIA

In a previous paper we expressed the opinion that postoperative complications affecting the central nervous system might follow the use of any general anesthetic agent. Indeed, under certain conditions cerebral anoxia may occur without operation or anesthesia. Thus transient hemiplegias, confusional psychoses and even convulsions may occur in cases of cardiac decompensation, diabetic acidosis or insulin shock or during infectious diseases. We have also elsewhere warned against the injudicious use of barbiturates and opium derivatives before and after operation. Recently McClure and his associates[9] have substantiated the soundness of this advice by a series of investigations on experimental animals and on patients.

In the hands of most anesthetists ether probably remains the safest general anesthetic agent, yet it is not without its dangers. In experimental animals the contractility and force of the heart beat are weakened, and yet a greater output of blood is demanded by the body.[10] Therefore the reserve of the heart is diminished. On the other hand, when death occurs during ether anesthesia respiratory depression is usually noted

7. Moon, V. H.: Shock and Related Capillary Phenomena, New York, Oxford University Press, 1938.

8. Weiss, S.; Wilkins, R. W., and Haynes, F. W.: The Nature of Circulatory Collapse Induced by Sodium Nitrite, J. Clin. Investigation **16**:73-84 (Jan.) 1937.

9. McClure, R. D.; Hartman, F. W.; Schnedorf, J. G., and Schelling, V.: Anoxia: Source of Possible Complications in Surgical Anesthesia, Ann. Surg. **110**:835-850 (Nov.) 1939.

10. Beecher, H. K.: The Physiology of Anesthesia, New York, Oxford University Press, 1938.

before circulatory disturbance is clinically very marked. It is well also to bear in mind that when administering ether by the open drop method and particularly through a machine it is possible to produce a high concentration of ether in the blood to the exclusion of a sufficient amount of oxygen. It is very probable that so-called "ether convulsions" occur on the basis of an associated anoxia, although many theories have been advanced to explain such convulsions.

The great danger, of course, so far as nitrogen monoxide is concerned, is the small amount of oxygen which can be given with it while a satisfactory degree of anesthesia is maintained for prolonged operations. It was felt at one time that nitrogen monoxide was the safest of all inhalation anesthetics, but this view can no longer be held with justice. Nitrogen monoxide itself produces no direct effect either on the heart or on the medullary centers; its dangerous effects are therefore probably due almost entirely to relative anoxia.

Ethylene and cyclopropane are useful gases because of the sufficient supply of oxygen which can be given with them. However, they are inflammable and explosive. Furthermore, cyclopropane may be definitely toxic to the myocardium, as is evidenced by cardiac arrhythmias, although, experimentally, Waters and Schmidt [11] showed that the respiration fails before the heart fails. It is true that the depth of respiration may be greatly diminished during cyclopropane anesthesia, possibly because of the high concentration of oxygen which can be given with the anesthetic gas. This may have its advantages for the surgeon, but it is not without danger to the patient. If the depth of respiration is insufficient to effect washing out of carbon dioxide from the venous blood, a paradoxic asphyxia of the tissues can occur in the presence of an abundance of available oxygen.

Avertin with amylene hydrate is a respiratory and circulatory depressant. Its use should always be accompanied by the administration of oxygen through a mask, a catheter or an intratracheal tube. Some patients seem particularly susceptible to its action, and at present there appears to be no way of telling which patient will be seriously depressed by a dose that would have simply an analgesic effect on other patients.

Spinal anesthesia is increasing in popularity for general abdominal procedures. This increasing popularity is certainly justified. However, it should be borne in mind that spinal anesthesia can produce marked circulatory depression by paralysis of the nerves which control vasoconstriction and that the anesthetic drugs may exert their effect on vital centers if the drug reaches too high. As a result, a fall in blood pressure and slowing of the pulse are commonly seen during spinal anesthesia.

11. Waters, R. M., and Schmidt, E. R.: Cyclopropane Anesthesia, J. A. M. A. **103**:975-983 (Sept. 29) 1934.

The routine use of the hypodermic administration of ephedrine sulfate or of neo-synephrin hydrochloride and the intravenous administration of dextrose in 5 per cent solution may prevent the fall in blood pressure or restore it to normal levels before any serious consequences result from the relative anoxia produced by such changes.

A source of possible danger in the administration of any of the various gas anesthetics is faulty apparatus. Every apparatus for administering anesthetic gases should be examined at regular and frequent intervals by a qualified expert. The dangers of using a machine with a defective valve are too great to allow this possibility to be overlooked. Such a machine may register a safe amount of oxygen flow while it is delivering an insufficient supply. Several tragic accidents have been reported as having occurred in this manner. Without doubt many more such accidents happen, although their true nature is unappreciated.

NUTRITIONAL DEFICIENCIES

Finally, we should be remiss if we failed to mention the role of vitamin deficiency in producing postoperative complication. The frequency of subclinical vitamin deficiencies has recently been stressed by Holman,[12] who showed that all patients who undergo elective operations benefit from the intensive administration of vitamins A, B, C and D for from forty-eight to seventy-two hours prior to operation and in the postoperative period.

In many cases nutritional deficiencies are sequels of organic disease, such as pyloric obstruction. Probably more frequently they are self imposed as a result of fads, diets, ignorance or economic want. In still other cases they are associated with chronic alcoholism. Whatever the underlying cause, the effect is very likely to make itself felt during the postoperative period. Vitamin B deficiencies are known to affect myocardial efficiency, and the importance of a competent myocardium has already been stressed. Vitamin C lack increases capillary permeability, which may predispose to shock. And so, in turn, the importance of an adequate blood level of each of the vitamins could be shown so far as postoperative complications are concerned.

CONCLUSIONS

After any presentation of the subject of cerebral complications after surgical operations, the statement is commonly made that such accidents are very uncommon. Indeed, surgeons of wide experience state that they have never seen such complications.

12. Holman, E.: Preoperative Precautions in the Prevention of Postoperative Pulmonary Complications, Internat. Abstr. Surg. **68**:335-339, 1939; Surg., Gynec. & Obst., April 1939.

It would be easier for us to believe that complications of the type we have described are seen all too frequently but that the exact nature of the complication and the manner of its production have not been fully appreciated. We have tried to emphasize that a multitude of conditions may be predisposing factors in the production of cerebral complications. Haldane [13] has stated that the human body is so constituted that no single organ can undergo damage save at the expense of the organism as a whole. Therefore, a seemingly unimportant disturbance of one system or one organ may assume great importance when the body is subjected to some unusual stress, such as an operation or administration of an anesthetic agent.

That many more accidents of this type occur than has been appreciated in the past has become apparent. There are many surgeons who have encountered cerebral complications following surgical operation and have been at a loss to explain them except on the grounds of cerebral embolism or thrombosis. Those careful enough to examine the brains of patients who die have frequently found that no embolism or thrombosis could be demonstrated. This left the manner of death in doubt. Such cases are rarely reported in the surgical literature; hence, recognition of this condition as a clinical entity has been slow.

Moynihan [14] said "Physiology, the fundamental science upon which medicine stands, is the meeting ground of physics and chemistry in their application to problems of function, both normal and aberrant, in man and animals." The influence of physiologic processes on the results of surgical operation has opened new fields for surgical investigation. In recent years much has been added to surgeons' knowledge as a result of such investigation, and the future will serve to uncover further evidence of the importance of this correlation.

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13. Haldane, J. S.: Respiration, New Haven, Conn., Yale University Press, 1922.

14. Moynihan, B. G. A.: The Advance of Medicine, New York, Oxford University Press, 1932.

PREOPERATIVE DIAGNOSIS OF TORSION OF THE PEDICLE OF THE SPLEEN

REPORT OF A CASE WITH SPLENECTOMY FOLLOWED BY RECOVERY

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The following case is worthy of being recorded on account of its rarity and the clinical features that led to a correct preoperative diagnosis.

REPORT OF CASE

Doris D., an East Indian girl aged 16 years, was admitted to the Colonna House Nursing Home on the evening of Sept. 8, 1938, with severe abdominal pain, intestinal obstruction and a visible tumor in the lower part of the abdomen.

She had had an attack of fever, similar to previous known attacks of malaria, which began at midday on August 3, five days before admission. Later in the same afternoon, without any apparent cause, she felt a pain in the right iliac fossa, at first mild but quickly becoming severe. The pain soon spread all over the abdomen. At about the time of onset of the pain she noticed a mass in the lower part of the abdomen, more prominent in the hypogastric region, which had not previously been there. The bowels moved during the day.

As she lived in a distant country district (Canje, County of Berbice), no medical advice was taken, and she was treated with home remedies. On the following day (August 4), she still had slight fever and vomited any food taken. The pain was still severe; the bowels moved. On August 5 the fever and vomiting had stopped. Severe abdominal pain continued. The bowels moved twice during the day. Similar conditions held on the next day, August 6. From this day on the bowels did not act, and the abdomen began to be slightly distended. On August 7 and 8, up to the time of her admission to the nursing home, the patient continued to suffer from very severe abdominal pain; there was absolute constipation, but no vomiting or retention of urine. Her general condition had been steadily deteriorating.

In the past history there was nothing of note apart from repeated attacks of malaria over a period of years. The patient stated that for a long time she had had a large spleen, which she had been able to feel through the abdominal wall, in the left hypochondrium.

Her menstrual history had always been normal (duration, three days; cycle, twenty-eight days). Her last regular period had been in the last week of May 1938. She was about two and a half months pregnant. The pregnancy was the first since her marriage.

Physical Examination.—The patient looked extremely ill. The temperature was normal; the pulse rate was 124 per minute; the respirations were rapid and shallow, numbering 28 per minute.

The general appearance was that of a well built young East Indian woman without any obvious abnormality. Although her face was drawn, she did not present the facies hippocratica. The color of the mucous membranes of the lips and tongue was normal; the conjunctivas showed no signs of anemia.

On examination of the various organs nothing unusual was found except in the breasts and in the abdomen. The breasts were well developed; the subcutaneous veins were marked, and the nipples and areolas, while they presented the appearances usually found in early pregnancy, were otherwise normal.

The abdomen was moderately and uniformly distended; no active peristaltic movements of the intestine could be seen. The lower part of the abdomen was filled by a large visible tumor, its upper limit in the midline reaching as high as the umbilicus. The percussion note over the tumor was completely dull; over the rest of the abdomen it was resonant. On palpation the tumor was found to be extremely hard and showed no signs of softening or fluctuation; its surface was smooth and its edges rounded. The tumor was slightly movable from side to side; any attempt to move it up or down caused great pain.

Below the umbilicus the abdomen was tender, and palpation of the tumor was very painful. In the upper part of the abdomen there was no tenderness, and even on deep palpation no muscular rigidity was elicited. There was no cutaneous hyperesthesia.

On vaginal examination the cervix was found to be soft; manipulation of the cervix did not cause pain. Although bimanual palpation of the uterus was impossible on account of the large abdominal tumor, the uterus appeared to be uniformly enlarged and soft. No resistance could be felt in the lateral fornices. The tumor appeared to rest on the fundus of the uterus but not to be attached to it. These findings were confirmed by rectal examination.

Careful examination of the left side of the hypochondrium by palpation, percussion and auscultatory percussion could not detect the presence of the spleen. The liver was normal in size and position.

The urine was free of albumin and sugar. There was no sediment on microscopic examination.

Differential Diagnosis.—The onset of the disease, with sudden pain in the right lower quadrant of the abdomen, was suggestive of acute appendicitis. This was easily excluded by the hypogastric tumor and by the clinical course of the disease during the five days before admission. In view of the two and a half months of amenorrhea, ectopic gestation had to be considered. This also appeared to be ruled out; there had been no vaginal bleeding at any time, and there were no signs of internal hemorrhage; the mass felt in the lower part of the abdomen was too uniform in contour and too solid to be a hematocele. On vaginal examination there was no tenderness of the cervix; there was no mass in either fornix, and the tumor appeared to be resting on the uterus, which was enlarged to the size usual with ten weeks' pregnancy.

The only diagnosis that could explain the symptoms and the clinical course of this acute abdominal condition appeared to be torsion of a mobile abdominal tumor on its pedicle. This involved consideration of the following possibilities: (1) a solid mesenteric tumor; (2) an ovarian cyst or tumor; (3) a pedunculated subserous fibroid, and (4) a prolapsed spleen.

Any one of these conditions, once torsion has taken place, can give rise to a similar clinical picture. The presence of a pedunculated subserous fibroid was

very improbable, as, apart from the youth of the patient, fibroids, while extremely common in Negroes, are exceptional in East Indians. In arriving at a differential diagnosis of the tumor, the only indications it was possible to consider were the symptoms caused by the presence of such a large mass in the abdomen before torsion took place. It was quite unlikely that such a mass should have existed unnoticed in the abdomen before onset of the acute condition.

The patient stated that she had never observed any tumor in the lower part of the abdomen before her present illness. But she was positive that she had long been subject to recurrent attacks of malaria and that she had a large spleen. Moreover, she lived in a highly malarial district, where the splenic index among East Indians is high. The tumor had the shape, size and consistency of an enlarged spleen, and careful examination of the left side of the hypochondrium could not detect the presence of this organ in its normal position.

It is pertinent to point out here that prolapse of the spleen, with or without torsion, is not as uncommon in this colony as in nonmalarial countries. If torsion of the pedicle is present the condition may give rise either to acute or to chronic symptoms. In the ordinary case of prolapsed spleen seen in this colony the spleen descends vertically, and the lower pole is found resting in the left iliac fossa, whereas when the spleen is merely greatly enlarged but not prolapsed the lower pole will be found at the umbilicus or stretching across into the right iliac fossa.

A diagnosis was therefore made of torsion of a suddenly prolapsed malarial spleen.

Operation.—On August 9, operation was performed with the use of spinal anesthesia. The abdomen was opened through a left paramedian incision extending from the hypogastrium to above the umbilicus. As was expected, when the peritoneum was opened a large spleen was found lying in the pelvis; its long axis lay transversely with the upper pole on the right side. The external and posterior surfaces looked upward and reached the level of the umbilicus. Some recent fibrinous adhesions between the spleen and the omentum, the transverse colon and loops of the small intestine were easily stripped off without any bleeding. A small quantity of free clear fluid in the lower part of the abdominal cavity was dried out with sponges. The large intestine was somewhat distended and hyperemic; once it had been freed from the adhesions, gas and feces were passed per anum (an event expedited by the spinal anesthesia), and the distention subsided.

There was no difficulty whatever in delivering the spleen through the wound, as the pedicle was greatly elongated. The pedicle had been completely twisted twice on its axis. The spleen, in addition to the enlargement due to malaria, was engorged with blood. The vessels in the pedicle were thrombosed; particularly noticeable was a large vein, distended and thrombosed, which pursued a serpiginous course between the layers of the gastrosplenic ligament, which was itself much stretched and elongated. There was a large, already clotted subcapsular hemorrhage at the hilus of the spleen.

The pedicle of the spleen, being wide and thick, was ligated and divided in sections, each section being secured by two ligatures, and the spleen was removed. The large thrombosed vein was also removed, together with part of the gastrosplenic ligament.

The size and appearance of the uterus were those associated with ten weeks' pregnancy; the organ was otherwise normal, and there were no adhesions between it and the spleen. After careful examination of the entire abdominal cavity, the abdomen was closed without drainage. The operation lasted approximately twenty-five minutes; the general condition of the patient was good.

The postoperative course was uneventful apart from two not unexpected incidents. One hour after the operation the patient had an attack of malarial fever, which reacted to 15 grains (0.97 Gm.) of quinine bihydrochloride given intramuscularly. She aborted on the eighth day after operation. She was discharged cured sixteen days after the operation.

Pathologic Picture.—The spleen weighed 2 pounds and 2 ounces (963 Gm.). The thrombosed vein in the gastrosplenic ligament, without untwisting its spirals, was 11 inches (28 cm.) long and ⅓ inch (0.8 cm.) in diameter. The main points

Fig. 1.—Lateral view of the spleen. Note the thrombus emerging from the sectioned splenic vein.

of note in the organ removed were: (1) the complete double rotation of the pedicle on its axis; (2) the subcapsular hemorrhage at the hilum, and (3) the extensive thrombosis of the vein in the gastrosplenic ligament.

No microscopic sections were made.

COMMENT

Rotation of the spleen on its pedicle is a very rare occurrence. The symptoms of the condition are such that the preoperative diagnosis is that of acute peritonitis, acute intestinal obstruction or, more commonly,

owing to the presence of a tumor lying in the pelvis, torsion of the pedicle of an ovarian cyst.

Torsion of the pedicle of the spleen is considered to be a complication of a wandering spleen. This condition occurs more frequently in women than in men, and its causes must be sought in some alteration of the peritoneal folds that form the suspensory ligaments of the spleen. Such an alteration may be due to a congenital elongation or to an

Fig. 2.—Spleen viewed from the hilus. Note the double torsion of the pedicle.

acquired one. An acquired elongation may result either from rupture of the peritoneal folds or from dragging on the folds from enlargement of the spleen. Repeated pregnancies are considered to be an etiologic factor in so far as they conduce to general visceroptosis and therefore to ptosis of the spleen.

The case described here is of particular interest on account of the youth of the patient; she was strong and well built, without any weakness of the abdominal wall. One etiologic factor appears to have been enlargement of the spleen due to malaria. There is no obvious reason

why the spleen should suddenly have prolapsed into the pelvis, rotating twice on its pedicle in its descent. It is suggested that the acute attack of malaria at the onset caused acute congestion of the spleen and an increase in the already abnormal weight of that organ and that the splenic ligaments, already elongated from either congenital or acquired causes, were unable to sustain the weight of the spleen.

Darfeuille [1] stated that the splenic ligaments cannot sustain a weight greater than 2.5 Kg. In this case the weight of the spleen removed

Fig. 3.—Thrombosis of the splenic vein.

was 2 pounds and 2 ounces, less than half the weight quoted from Darfeuille. However, it is possible that when the ligaments of the spleen are stretched and elongated, as they were in this case, they may be able to sustain a lesser weight than is normal. No sign of laceration of the ligaments was observed at operation.

1. Darfeuille, C.: Deplacements de la rate avec torsion du pédicule, Thesis. Paris, no. 3, 1894.

During the descent of the spleen into the pelvis, as described by Childe,[2] the upper pole, on account of its greater size and the normally oblique position occupied by the spleen in the left hypochondrium, is the first to tip forward toward the midline, thereby causing rotation of the pedicle from left to right. The farther the upper pole descends, the greater will be the torsion of the pedicle. Once the spleen has lost its normal position and lies free in the abdominal cavity, peristaltic movements of the intestines may cause further rotation.

2. Childe, C. P.: Wandering Spleen: Haemorrhage Within the Capsule; Splenectomy; Recovery, Brit. M. J. **2**:1631, 1903.

SEVENTY-SECOND REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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CONGENITAL DEFORMITIES

Congenital Bowing and Pseudarthrosis of the Lower Part of the Leg.—Pseudarthrosis following fracture or osteoclasis during childhood in cases of congenital bowing of the lower part of the leg has been observed frequently, but its association with von Recklinghausen's neurofibromatosis has not been reported in the English literature. Barber [1] reports 5 cases, in 4 of which there was definite bending of the lower part of the leg present at birth. In 1 case, fracture and operative intervention were avoided, with the result that no functional handicap now exists. In fact, some improvement in the degree of angulation took place with growth. Osteotomy, osteoclasis and fracture were each followed by pseudarthrosis in 3 cases. In 1 case, in which no history of bending could be obtained, pseudarthrosis followed fracture. In all of these cases typical lesions of von Recklinghausen's disease were present.

Frequency of Congenital Deformities in Families.—An editorial in *The Journal of the American Medical Association* [2] reviews a study by

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This report of progress in orthopedic surgery is based on a review of 116 articles selected from 138 titles pertaining to orthopedic surgery and appearing in the medical literature approximately between Nov. 1, 1939, and March 1, 1940.

1. Barber, C. G.: Surg., Gynec. & Obst. **69**:618, 1939.

2. Frequency of Congenital Malformations in Families, editorial, J. A. M. A. **114**:141 (Jan. 13) 1940.

Murphy of statistics in Philadelphia for a period of five years. It was found that gross congenital malformations afflict 1 of every 213 persons who are born alive. The rate is twice as high among white persons as among Negroes. The frequency of birth of subsequent malformed offspring was twenty-five times greater in families already possessing a malformed child than in the general population. The investigations lead to the conclusion that gross congenital malformations arise solely from influences which affect the germ cells prior to fertilization. No relation was demonstrated between frequency of malformation and such factors as illegitimacy, economic or social status or chronic disease at the time of conception.

[ED. NOTE: Earlier studies were reviewed in previous reports of progress.]

Muscular and Skeletal Changes in Arachnodactyly.—The syndrome arachnodactyly (spider digits) is discussed in detail, and 6 cases illustrating various features of the syndrome are reported.[3] The cause of the condition is obscure, but there is a family history of the lesion in over half of the cases reported. The abnormalities associated with arachnodactyly are not ordinarily detected until the second or third year of life. In all cases there is a decrease of soft tissue in some portion of the body and hence an actual or apparent lengthening of the hands and feet, particularly the fingers and toes. The face may have an appearance of maturity because of a decrease of subcutaneous tissue. Muscular weakness is proportional to the size of the underdeveloped muscles. Microscopic examination of muscle from 2 patients showed normal muscular tissue. Ligamentous relaxation is always present and is usually most pronounced in the joints of the hands and feet. Subluxation of the sternoclavicular joint and dislocation of the patella have been reported. When contractures occur, the fingers and toes are usually involved, but occasionally only the larger joints are affected. Persons with arachnodactyly usually have contractures, but occasionally only the larger joints are affected. Persons with arachnodactyly are usually taller than normal persons and weigh less. They commonly have a spinal deformity, scoliosis, kyphosis or kyphoscoliosis, which appears in early life and slowly progresses but in most cases does not become severe. Dolichocephalus, prognathism, a narrow-arched palate and asymmetry of the skull are common anomalies. Heart disease, usually on a congenital basis, is a frequent accompaniment of the disease. The ophthalmologic features are those associated with ectopia lentis, iridodonesis, contracted pupils and irregularity of the anterior chamber of the eye. Bilateral dislocation of the lenses is an outstanding symptom. Improvement of vision

3. Fahey, J. J.: Muscular and Skeletal Changes in Arachnodactyly, Arch. Surg. **39**:741 (Nov.) 1939.

usually results from removal of the lens in cases in which it is completely dislocated. Pain in the foot may necessitate the use of supports. Contracture of the fingers may be treated, with improvement in function.

[ED. NOTE: There are wide variations in the amount of deformity presented. Many patients show the changes only in the hands and feet.]

DEVELOPMENTAL DISEASES

Epiphysitis of the Spine.—Nathan and Kuhns [4] feel that this condition is a relatively common lesion. Sixty-nine of the 75 cases studied were observed during the past six years. Most of the patients visited the hospital for the treatment of faulty posture. The roentgen studies revealed irregularity of the upper and lower surfaces of the vertebral bodies to be the most constant finding. The late changes were constantly found to consist of anterior wedging of the vertebral bodies. Under treatment the deformity was decreased but rarely corrected. Deformity was prevented in only 2 cases. Treatment usually consisted of application of a plaster jacket with the spine in extension; in addition, corrective exercises were given. In the early acute stages of the disease, recumbency in a plaster shell with the spine in extension, which was carried out in only 5 cases, seemed to be the most efficient form of treatment. In adult patients who had had no previous treatment, severe deformity associated with pain and weakness in the back was usually present.

Late Impairment of the Spinal Cord in Scheuermann's Juvenile Kyphosis (Spinal Epiphysitis).—Wretblad [5] reports on 6 patients, all young men engaged in hard physical labor, who had juvenile kyphosis. In these patients symptoms of medullary irritation and compression developed. As a rule the symptoms appeared first on one side and later on the other. Numbness, weakness and unsteadiness in the legs were observed. Spastic paralysis of the legs was present in several cases. Myelographic study revealed a block at the apex of the curve. Laminectomy led to improvement in 3 patients whose symptoms had been of short duration. Another, in whom symptoms had been present several years, died after laminectomy. In this case autopsy showed that irreparable damage had occurred to the spinal cord.

Pectus Excavatum.—Brown [6] states that pectus excavatum is characterized by a funnel-shaped depression of the sternum, the apex of which is located at the junction of the xiphoid process with the gladiolus. Prevention or correction of this deformity is indicated because of definite functional restrictions on the circulatory and respiratory mechanisms and, in women, for esthetic purposes. The diaphragm is the chief

4. Nathan, L., and Kuhns, J. G.: J. Bone & Joint Surg. **22**:55, 1940.
5. Wretblad, G.: Acta psychiat. et neurol. **14**:617, 1939.
6. Brown, A. L.: J. Thoracic Surg. **9**:164, 1939.

deforming factor, since, with its attachment to the lower part of the sternum, it is the only muscular force capable of drawing the sternum inward with the point of maximum indentation at the sternoxiphoid junction. A strong factor in maintaining deformity is the substernal ligament, which is continuous with the linea alba in the abdomen. The heart may be fixed in the midline, resulting in encroachment and cardiac embarrassment, or it may be displaced to the right or to the left, with no resulting disturbance. There is a strong hereditary factor in this deformity. Treatment for the adult consists of elevation of the depressed portions of the sternum, cartilages and ribs to correct the obvious skeletal deformity. However, the contracted and depressed substernal ligament must also be sectioned to allow for extension of the chest on the abdomen and for correction of the round-shouldered habitus. In early childhood the simple procedure of section of the substernal ligament and freeing of the sternal attachment of the diaphragm is sufficient to prevent full development of the deformity.

[ED. NOTE: In children, improvement in this condition is observed with respiratory exercises. The editors have had no experience with operative section of the substernal ligament.]

NUTRITIONAL DISTURBANCES OF BONE

Osseous Dystrophy Following Severe Icterus Neonatorum.—Braid [7] reports the cases of 2 patients with severe jaundice at birth who showed osseous dystrophy, pathologic pigmentation of the skin and sexual precociousness. The author believes that damage occurs to the liver, interfering with the storage and utilization of vitamins. The first patient, a youth of 19, had had bony deformity since the age of 2. There were kyphosis, deformity of the chest and deformity of the leg. Laboratory studies carried over a number of years showed a relatively low level of blood calcium. Biopsy showed irregular trabeculation of the bones, with vascular fibrous tissue in the interstices resembling osteitis. The roentgenograms showed cystic changes at the ends of the diaphyses, with numerous old fractures. The second patient was a girl aged 2 years. The osseous appearance was similar to that in the first case.

Osteomalacia of the Spinal Column from Deficient Diet or from Disease of the Digestive Tract.—Meulengracht [8] records the cases of 6 patients living in Denmark in whom osteomalacia of the spinal column developed as the result of deficient diet or after gastrointestinal disease. There were 4 others who had the same condition from an excessive use of laxatives. From his studies the author feels that the diet of the adult population is deficient in calcium and in vitamin D. All of

7. Braid, F.: Arch. Dis. Childhood **14**:181, 1939.
8. Meulengracht, E.: Acta med. Scandinav. **101**:138, 1939.

these patients were past middle age. Treatment consisted of support to the back and the addition of vitamin D and calcium to the diet.

TUBERCULOSIS

Extra-Articular Foci in Tuberculous Arthritis.—Fifty-five cases of extra-articular tuberculosis of the hip joint in children are reviewed by Cholmeley.[9] The commonest sites were in the medial half of the acetabular roof (19 cases) and in the femoral neck (17 cases). Twelve children were treated by excision of the focus or by curettage; the remaining 43 were treated purely conservatively. Of these 43, only 3 escaped involvement of the hip joint (7 per cent); of the 12 operated on, only 1 (8.3 per cent) escaped involvement. The average time that elapsed before involvement of the hip could be demonstrated was about seventeen months in each series. It is concluded that less than 10 per cent of children with extra-articular foci around the hip recover with an intact hip joint.

Pott's Disease in Children.—Smith [10] reports an analysis of 81 cases of tuberculosis of the spine treated in Sydney, Australia. Of the 81 patients, 17 could not be traced. Fifteen had been recently observed; 12 had died, and 2 were cured. There were 7 who were almost without symptoms but could not do all of their usual activities. Their condition was called insecure fibrous union. There were 18 in whom the disease was still active or had become active again. Spinal fusion was performed on 10. In 6 of these abscesses developed after operation; 5 suffered from an increase of the deformity, and 2 became paraplegic. The author states that stabilizing operations are contraindicated for children with active disease and that stability of the kyphos is dependent on vertebral contact.

[Ed. Note: This gloomy view of the ineffectiveness of spinal fusion is not held in America. The recent report of Swett suggests that complete healing occurs only in the presence of vertebral contact.]

Tuberculous Spondylitis.—Walheim [11] studied 221 cases of tuberculosis of the spine in children observed at St. Görans Hospital, Stockholm. One hundred and forty-nine children were treated operatively (method of Albee). Fifty per cent of the children were under 10 years of age. Two or more vertebrae were involved in 90 per cent of the cases. Gibbus was found in over 90 per cent of the patients. Abscesses were found in 60 per cent, and fistulas, in 25 per cent. Paralysis occurred in 6 per cent. Death occurred in 60 cases, in 31 from spondylitis directly; in 20, from other types of tuberculosis, and in 9, from non-

9. Cholmeley, J. A.: Brit. J. Surg. **27**:224, 1939.
10. Smith, G. K.: M. J. Australia **2**:303, 1939.
11. Walheim, T.: Acta chir. Scandinav. **83**:123, 1939.

tuberculous diseases. Of these 123 living operatively treated patients, 91 are entirely well; 18 have slight trouble with their backs, and 1 is unable to work. Of the 34 living conservatively treated patients, 25 are well, 8 have slight trouble with their backs, and 1 is unable to work. The functional ability is distinctly better in the backs of the patients operated on. The time spent at the hospital was longer for those operated on. The active disease lasted longer in those conservatively treated. A greater tendency to recurrence of the disease was observed in the conservatively treated patients.

SYPHILIS

Syphilis of the Skeleton in Early Infancy.—Caffey [12] studied roentgenograms of the skeletons of 550 young infants who did not have syphilis. In 22 cases the roentgenograms showed changes indistinguishable from syphilitic osteochondritis, osteoperiostitis and osteomyelitis. Caffey concludes that the roentgen findings in the skeleton per se are not conclusively diagnostic of early infantile syphilis.

GONOCOCCIC ARTHRITIS

Gonococcic Arthritis in the Newborn.—Parrish, Console and Battaglia [13] present a case of gonococcic arthritis in a newborn Negro treated with sulfanilamide. The mother had migratory articular pains one week before delivery and a profuse vaginal discharge at the time of delivery. When the child, a boy, was 3½ weeks old, he was brought to the hospital with a swollen, warm, tender, flexed left knee. Aspiration showed thick pus, from which gonococci were cultured. Sulfanilamide was given, and the swelling, pain and tenderness diminished by the fourteenth day in the hospital but recurred when the drug was withdrawn. Therapy was again instituted, and the swelling subsided in four days and did not recur when the drug was discontinued. A short review of the literature, showing the frequency of this disease in the newborn, is presented.

BACK

Sacroiliac Changes in the Diagnosis of Spondylarthritis in the Early Stages.—In an examination of 153 cases of ankylosing spondylarthritis, Forestier [14] found that the sacroiliac joints were involved in 98 per cent. In 12 instances observed in the early stages of the disease he found the sacroiliac joints roentgenographically involved prior to any changes in the spine. The reverse was not observed. Hence the author emphasizes the importance of sacroiliac changes in the early diagnosis of

12. Caffey, J.: Am. J. Roentgenol. **42**:637, 1939.

13. Parrish, P. P.; Console, W. A., and Battaglia, J.: Gonococcic Arthritis of Newborn Treated with Sulfanilamide, J. A. M. A. **114**:241 (Jan. 20) 1940.

14. Forestier, J.: Radiology **33**:389, 1939.

ankylosing spondylarthritis. These changes consist of marginal decalcification followed by a spotted, mottled appearance of the cancellous bone and later by loss of joint space and synostosis.

Intraspinal Lesions Associated with Pain Low in the Back and Sciatic Pain.—Camp and Addington [15] report their observations based on 417 cases in which iodized poppyseed oil was injected into the spinal subarachnoid space for the purpose of localizing a suspected lesion affecting the spinal cord or the cauda equina. In 283 of these cases (67.9 per cent) subsequent laminectomy was performed. The positive diagnoses were as follows: tumor of the cord, 45 cases; protruded intervertebral disk, 208 cases; hypertrophied ligamentum flavum without protrusion of the disk, 6 cases, and miscellaneous conditions, 32 cases. The examination was reported giving negative results in 126 cases, or 30 per cent. Thirteen of the patients were operated on in spite of the negative results. A protruded disk was found in 7 of these cases, hypertrophy of the ligamentum flavum in 4 and no lesion in 8. The authors express the belief that iodized poppyseed oil gives more accurate results than does air, that it will reveal certain structures not seen with air and that it has localized lesions that air has failed to disclose.

Air Myelography in the Diagnosis of Intraspinal Lesions.—Chamberlain and Young [16] report their experience with air or oxygen myelography in over 150 cases of pain low in the back or sciatic pain. In over half of these cases the lumbocaudal sac was studied. There were positive findings in this region after injection of air in 10 patients. All of these came to operation, and in each the uncovered lesion was at the exact level demonstrated by the roentgenograms. From 30 to 50 cc. of air was used to fill the lumbocaudal sac in adults. When the Queckenstedt test shows either complete or partial block, 4 to 6 cc. of air is injected below the suspected lesion, and stereoroentgenograms are taken with the patient in the upright position. The authors demonstrated complete block in the lumbocaudal sac in 3 patients; 2 of these had tumors, and 1 showed herniated cartilaginous disk.

Neurologic Aspects of Herniated Nucleus Pulposus.—Spurling and Bradford,[17] on the basis of 85 low intraspinal lesions treated surgically, present what they have found to be a characteristic clinical picture of herniated nucleus pulposus at the fourth and fifth lumbar interspaces. Briefly, the symptoms and signs include severe, persistent sciatic pain, paresthesias (which are far more localizing than is the distribution of

15. Camp, J. D., and Addington, E. A.: Radiology **33**:701, 1939.

16. Chamberlain, W. E., and Young, B. R.: Radiology **33**:695, 1939.

17. Spurling, R. G., and Bradford, F. K.: Neurologic Aspects of Herniated Nucleus Pulposus at Fourth and Fifth Lumbar Interspaces, J. A. M. A. **113**: 2019 (Dec. 2) 1939.

the pain), stiffness of the lumbar part of the spine, a positive Laségue sign, hyperesthesia of the foot and of the lateral aspect of the leg and diminution or absence of the ankle jerk. They feel that a more thorough experience with the neurologic picture has made possible accurate diagnosis from clinical evidence alone in the majority of instances. These signs are not peculiar to this entity, since neoplasms along the course of the sciatic nerve, pelvic and rectal disease and disease of the osseous structures may simulate the clinical picture.

Sciatic Radiation of Pain Low in the Back.—Steindler [18] attempts to explain the lesion in cases of low back pain on an anatomic basis. This is possible because there exists in cases of pain low in the back a so-called trigger point. For example, in cases of the lumbosacral syndrome this point exists at the lumbosacral junction; in cases of the tensor fasciae latae syndrome the tender point is at the lateral border of the fascia and iliotibial band, with a positive Ober sign. The author states that sciatic radiation of pain in a large group of cases has nothing whatever to do with direct irritation either of the nerve trunk or of its roots but is purely a reflex phenomenon which follows, instead of preceding, pain in the lower part of the back. Furthermore, it is the author's belief that the afferent branch of the reflex arc is furnished by the sensory fibers supplying the injured muscular and aponeurotic structures and that the connection with the sciatic nerve is made not lower than the spinal ganglion and possibly in the spinal cord. To prove the reflex character of this radiation, the author first shows that anatomically the territory involved is entirely separate from the origin of the sciatic nerve. The proof which establishes the causal connection between the local lesion and the sciatic radiation rests on the fact that irritation of the so-called trigger joint exaggerates the sciatic radiation, whereas injection of procaine hydrochloride at this point reduces the local pain as well as the sciatic irritation. In 100 cases the author, with the assistance of Dr. J. V. Luck, found that the test gave a positive result in 69 and a negative result in 31. Of the 69 cases in which it gave a positive result, the end results were good in 84 per cent and poor in 16 per cent, whereas of the 31 cases in which the result was negative, the end results were good in 20 per cent and poor in 80 per cent. The authors feel that in a considerable proportion of cases of radiating pain low in the back recognition of the reflex character of the radiation of pain is essential to rational diagnosis and treatment of the condition.

Spondylolisthesis.—Hitchcock [19] presents 3 cases of spondylolisthesis, with roentgenograms and case histories. Roentgen evidence of progressive slipping of the fifth lumbar vertebra on the sacrum is presented.

18. Steindler, A.: J. Bone & Joint Surg. **22**:28, 1940.
19. Hitchcock, H. H.: J. Bone & Joint Surg. **22**:1, 1940.

In trying to explain the cause of this condition the author states that trauma during delivery or shortly after may be the cause of this defect. His belief is based on observations made on stillborn infants, on whom he was able to demonstrate fractures of the neural arch in the lumbar region by hyperflexion, such as might occur during labor or delivery, whereas hyperextension did not result in a fracture of the neural arch. Furthermore, the author cites studies by Willis, Hayek and others, who failed to find, in spite of deliberate search, a single example of separation either of anomalous centers of ossification or imperfect ossification which would correspond with such a defect in the neural arch. This study was based on a collection by the various authors mentioned of over 2,000 spines. Spondylolisthesis therefore appears to be the result of trauma rather than of congenital defects.

Scoliosis Following Empyema.—Scoliosis resulting from pulmonary disease is usually of one of two types:[20] 1. Scoliosis following empyema —the concavity is toward the empyema, and there is little or no rotation of vertebral bodies. 2. Scoliosis complicating thoracoplasy—the convexity is toward the resected ribs. In a survey of 65 cases of empyema operated on in the years 1932 to 1936 inclusive at Mount Sinai Hospital, New York, none of 52 patients with acute empyema whose wounds healed permanently in a mean time of four months or less had persistent scoliosis. Of 13 patients with chronic empyema requiring multiple operations, rib resections and excisions of the soft parts, persistent scoliosis developed in 5. These 5 were 12 years old or under, and only 2 showed scoliosis so marked as not to be hidden by clothing. These 2 are discussed in detail. The most severe scoliosis was a 97 degree curve, which followed a thoracoplasty at the age of 12 years for chronic empyema. The scoliosis was of the usual thoracoplasty pattern, with the convexity on the side of operation and with considerable rotation of the vertebral bodies. Treatment with various types of jackets was of no avail. In the other case, severe scoliosis followed chronic empyema for which operation was first performed at 2 years of age. The curvature progressed in spite of treatment. The curve was of the postempyemic type, with the concavity toward the diseased side and without rotation.

NEOPLASMS

Multiple Myeloma.—This disease, a multiple neoplastic disease of bone marrow or a diffuse hyperplasia, usually of cells resembling plasma cells, is discussed by Ulrich.[21] In 259 case histories of multiple myeloma it was found that absence of pain was rare (4 per cent). Roentgen

20. Selig, S., and Arnheim, E.: Scoliosis Following Empyema, Arch. Surg. **39**:789 (Nov.) 1939.

21. Ulrich, H.: Multiple Myeloma, Arch. Int. Med. **64**:994 (Nov.) 1939.

evidence of tumor was present in 96.9 per cent. Bence Jones protein was absent in 38.2 per cent. Bence Jones protein is not a single substance but rather a group of similar, but not identical, proteins, and this complexity may have a bearing on the difficulties of determining its presence under certain circumstances. The effect of this disease on the kidneys is to produce obstruction of the tubules by formation of tubular casts of Bence Jones protein. Extraosseous myeloma is not uncommon. The four possibilities of origin are by direct extension from intraosseous tumor, by metastasis, by independent development and by growth of a primary extramedullary tumor. Direct extension and metastasis are the most common sources. The nature of myeloma cells has been much disputed. In most cases the cells resemble plasma cells more closely than any other known form of cell. There are, however, frequent variations. The origin of all of these different types of cells is probably from a single type of myeloid cell. In its relation to leukemia, multiple myeloma is a neoplastic disease occupying a position midway between frank tumors and diffuse leukemic hyperplasia. The author reports 1 case with certain noteworthy features, consisting of tumors in the testes, absence of pain, absence of roentgen evidence of abnormality in the bones and the presence of myeloma cells in the circulating blood.

Eighty-six cases studied by Ghormley and Pollock [22] were divided into 5 groups, as follows. Group A: 19 cases in which the diagnosis was proved by postmortem examination. Group B: 53 cases in which the diagnosis was made on a basis of clinical and roentgen findings (all of the patients in groups A and B have died). Group C: 5 cases in which the diagnosis was made on clinical and roentgen evidence. No follow-up record had been received from the patients in this group, though it is assumed that they were dead. Group D: The patients in this group, proved by biopsy to have multiple myeloma, are still alive. Group E: 3 patients still alive one year or more after the original diagnosis was made. The diagnosis here was made on the basis of clinical and roentgen findings. A detailed study of the cases of group D is appended. The average duration of the disease in all cases was twenty-six and nine-tenths months; in the proved case, twenty-six and eight-tenths months. Bence Jones proteinuria was present in only 51 per cent of the entire group. The albumin-globulin ratio was reversed in only 50 per cent of the cases, and in the series of proved cases none of these reactions were positive. The same may be said of the reactions for calcium, phosphorus, phosphatase and the determinations of basophilia or eosinophilia. Regarding the prognosis, although 2 patients are alive five and eight years respectively after the onset of the disease, the outlook for patients who have involvement of the bone is uniformly

22. Ghormley, R. R., and Pollock, G. A.: Surg., Gynec. & Obst. **69**:648, 1939.

poor. In 1 case involvement of the soft parts only was present. Treatment of multiple myeloma is doomed to failure from the beginning.

Treatment of Osteogenic Sarcoma.—A study of 258 cases of osteogenic sarcoma treated by amputation selected from the first 400 cases in the Registry of Bone Sarcoma of the American College of Surgeons revealed that early amputation tends to hasten a fatal outcome.[23] Early amputation is interpreted as amputation within six months of the onset of symptoms. Survivors are defined as patients living with no evidence of tumor at the last report, more than five years after amputation, and the last surgical treatment. Only 8 per cent survived early amputation, whereas 29 per cent survived later amputation. In cases of sarcoma of a lesser degree of malignancy, 14 per cent of patients survived early amputation and 41 per cent survived delayed amputation. In cases of sarcoma of unusually high malignancy, 4 per cent of patients survived early amputation, and 37 per cent survived delayed amputation. When the cases of sarcoma of possibly low malignancy are excluded from among the cases of late amputation, 24 per cent of the patients in the remaining cases survived. This figure is three times as great as that for early amputation. The author feels that radiation is one means by which the development of recurrence after excision may be retarded. Also, he states that in the few cases in which bone grafts were inserted at the sites of excision of osteogenic sarcomas the development of recurrence was retarded. He believes that the bone graft occupies space which would otherwise be partly occupied by blood clot from which the fibrin might nourish or even stimulate fibroblastic cells. Also, the inserted bone stimulates the endothelial leukocytes which might retard the growth of the tumor cells. In conclusion, stress is laid on avoidance of early amputation and on irradiation before amputation or excision and implantation of a bone graft.

Benign Chondromas of Ribs.—This is a review ot the cases from the literature of benign chondromas of the ribs proved by biopsy or excision, together with 2 case reports.[24] There are various theories concerning the cause, the most probable being that the tumors arise from either cartilaginous fetal rests or islands of cartilage resulting from old rickets. Trauma seems to be significant in some of the reported cases. These tumors usually start insidiously and are of long duration. In regard to the pathologic picture, the benign central chondroma is a transition between osteochondroma and malignant chondromyxosarcoma. Adult cartilage predominates in its histologic picture. Changes may occur during development, so that the chondroma may become osseous chondroma or may undergo malignant degeneration to become a

23. Ferguson, A. F.: J. Bone & Joint Surg. **22**:92, 1940.
24. Harper, F. R.: J. Thoracic Surg. **9**:132, 1939.

chondromyxosarcoma. The author states that there is a strong tendency for a high benign chondroma to undergo malignant degeneration. Therefore, chondromas in the ribs are potentially malignant even though they may appear histologically benign. Clinically a sudden increase in size of the tumor or an increase in the pain may indicate a turn toward malignancy. Benign chondromas are very prone to recur, and incomplete removal seems to stimulate growth of the remaining tissue. In 5 of 11 cases followed more than one year, the tumors recurred. Treatment should consist of early and complete removal of the tumor. It is often necessary to open or resect part of the pleura for complete removal. Some authors advise radium or roentgen therapy after the operation.

SHOULDER

Traumatic Dislocation of the Tendon of the Biceps Brachii Muscle.—Abbott and Saunders [25] state that attritional changes play a part in dislocation of the tendon of the biceps brachii muscle but cannot ignore the definite and severe accidents associated with each of their cases. They feel that forcible lateral rotation of the arm is the principal cause of dislocation. The injury is followed by pain and swelling of the joint, with complete disability of the affected shoulder. Weakness and limitation of motion in forward flexion and adduction of the shoulder are present, and forced supination of the forearm against resistance with the elbow held in flexion is painful. The principal findings include swelling of the anterior aspect of the shoulder, tenderness (most pronounced over the bicipital groove) and a definite snapping sensation on abduction and external rotation of the shoulder. In all of the 6 cases, which are reported in some detail, operation disclosed displacement of the tendon over the lesser tuberosity. Fixation of the tendon in the bicipital groove is probably the quickest and best method of restoring function in a case of uncomplicated dislocation, but no rules as to the best procedure have been adopted. Adequate results may be obtained by replacement of the tendon and repair by fascia of the roof of its groove.

Echinococcus Cyst of the Shoulder Joint.—Karageorgis [26] reports a case of echinococcus cyst of the shoulder joint capsule. The patient was a 25 year old woman who for three years had suffered with articular pain and for two years with swelling. The condition was diagnosed first as rheumatism, then as tuberculosis and finally as lipoma or foreign body reaction. A posterior approach resulted in exposure of the cyst inside the joint capsule. The cyst was filled with dead daughter cysts. The postoperative course was uneventful, and the patient apparently recovered. In Greece, 1 other echinococcus cyst of the shoulder joint and 1 echinococcus cyst of the hip joint have been reported.

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25. Abbott, L. C., and Saunders, J. D. de C. M.: Surgery **6**:817, 1940.
26. Karageorgis, B.: Zentralbl. f. Chir. **66**:2006, 1939.

KNEE

Chondritis of the Knee.—Darrach [27] summarizes 376 arthrotomies of the knee for internal derangement. In 27.1 per cent of cases the anterior cruciate ligament was found to be partially or completely ruptured. In 51 per cent there was involvement of the articular cartilage. In 6.8 per cent of the cases in which it was present it was the only demonstrable lesion. Darrach stated: "In the majority of instances this condition involves only the superficial portion of the articular cartilage, and rarely does one see the underlying bone exposed." The term chondritis is suggested for this lesion, since osteochondritis applies only to conditions including involvement of bone. An incision large enough to enable one to explore the knee joint more thoroughly is advocated. The affected areas of cartilage are treated by shaving them off with a knife or a sharp gouge, leaving as smooth a surface as possible.

Suppurative Arthritis of the Knee.—Maurer [28] reports 26 cases of suppurative arthritis of the knee joint treated in the Munich clinic in recent years. In all but 6 the condition followed direct injuries involving the joint (9 cases), the patella (7 cases), the femur (1 case) or the tibia (2 cases). In all cases a phlegmon of the capsule developed. Thirteen phlegmons were due to the streptococcus and 4 to the staphylococcus; 3 were due to a mixed infection. One was due to the pneumococcus. They were treated essentially by incision and drainage (anteriorly bilateral, and medioposterior incisions), followed by instillation of Chlumsky's phenol-camphor solution (phenol, 30 per cent; camphor, 60 per cent; alcohol, 10 per cent). Immobilization was stressed. Complications necessitated resection of condyles (5 cases), amputations (7 cases, with 3 deaths) and secondary closure (9 cases). In all, 4 patients (15.4 per cent) died of general infection. Blood transfusions were liberally resorted to. The end results in 26 cases were: 3 joints with slight motion, 14 stiff joints, 4 thigh amputations, 4 patients dead and 1 unknown result.

[ED. NOTE: While a perfect result is rarely expected after suppurative arthritis of the knee joint, a better showing is usually made by those patients who are treated by adequate drainage and early motion.]

FOOT

Feet of Infants and Children.—Bloxsom [29] briefly reviews his records of footprints and heelprints showing the development of the longitudinal arch in 473 infants and children from 1 to 12 years of age. The rate

27. Darrach, W.: Ann. Surg. **110**:948, 1939.

28. Maurer, G.: Arch. f. klin. Chir. **197**:639, 1939.

29. Bloxsom, A.: Study of Feet of Infants and Children, Am. J. Dis. Child. **59**:45 (Jan.) 1940.

of development of the foot and its longitudinal arch varies considerably, but growth usually progresses most rapidly in children from 1 through 4 years of age. There are a certain number of children whose feet continue in a nondeveloping stage, and it has been found that corrective measures applied to these feet over years do no good. The author believes that the recording of footprints and heelprints of children is a valuable aid to the pediatrician.

INJURIES TO JOINTS

Rarefaction of Bone After Injury to Joints.—Jaffe [30] reports 2 cases in which an acute trauma (without fracture) to a large joint resulted in severe rarefaction in the adjacent long bones. In 1 case the changes in the lower end of the femur were considered malignant, and the leg was amputated. In the other a biopsy specimen was taken from the lower end of the humerus, and the diagnosis of post-traumatic rarefaction was established. The roentgenogram shows round areas of rarefaction extending from just beneath the joint surface well into the medulla. The changes are probably due to a neurovascular derangement which with numerous dilated and engorged blood vessels results in localized bony rarefaction. Recovery is favored by active use of the part, with diathermy and massage.

Painful Atrophy of Joints.—Ghormley [31] describes the clinical picture, diagnosis and treatment of post-traumatic painful atrophy of joints. The writer states that there may be considered to exist three types of atrophy: (1) Sudeck's "reflex" atrophy; (2) post-traumatic painful atrophy of joints, and (3) atrophy of disease. Post-traumatic painful atrophy of joints "may be regarded as a clinical entity perhaps as a variation of Sudeck's atrophy, although often its onset is slower than that of Sudeck's atrophy, and the symptoms are much less severe." One case is presented, in which arthrodesis of the knee was performed and led to a satisfactory outcome. This case offered material for study, which revealed marked bone atrophy, a dry joint and slight thickening of the synovial membrane, with a definite pannus-like membrane covering a portion of the surface of the joint. There were thinning of the articular cartilage and absence of all marrow elements. In addition to the known methods of treatment, administration of vitamin D and calcium is considered beneficial.

MISCELLANEOUS

Gas Gangrene.—Williams and Hartzell [32] compare mortality statistics in cases of gas gangrene in San Francisco. In these cases the diagnosis

30. Jaffe, H. L.: Radiology **33**:305, 1939.
31. Ghormley, R. K.: Arch. Phys. Therapy **20**:725, 1939.
32. Williams, A. J., and Hartzell, H. V.: West. J. Surg. **47**:56, 1939.

was proved clinically, bacteriologically and by roentgenograms. In the first series, treated from 1934 to 1937, the mortality rate was 58.3 per cent. In the second series, treated from 1936 to 1939, with benefit of roentgen therapy, the mortality rate was 8.3 per cent. In the series of 12 cases in which roentgen therapy was used, there were 4 patients who required amputation. Amputation was performed after roentgen therapy, and at the time of amputation no gas was noted in the soft tissues. Eight cases of arteriosclerotic gangrene complicated by gas gangrene are included. Four of the patients were treated with roentgen therapy, and 4 were not. All these patients died. Those that were treated with roentgen therapy showed no gas in the tissues at death. Of those who died after roentgen therapy 2 died of pulmonary embolism, 1 of pneumonia and 1 of arteriosclerotic heart disease. Two of the untreated patients died of gas gangrene.

FRACTURES AND DISLOCATIONS

New Clavicular Splint.—A new type of clavicular splint applying the principle of suspension-elevation is used by Anderson [33] to treat fractures of the clavicle along correct anatomic and physiologic lines. At the same time it allows the patient to be up and about, wearing his usual clothing and retaining the use of both arms. The author states that convalescence is painless and that the splint is comfortable. Many patients return to work a few days after injury, and skilled and professional workers have continued to work regularly with the splint in place. The splint consists of (1) a body frame or base and (2) a rubber suspension axillary hammock. The advantage is saving of time and expense to both the patient and the physician.

Injury of the Acromioclavicular and Sternoclavicular Joints.—Howard [34] reviews the salient features of anatomy, function and disability of the acromioclavicular and sternoclavicular joints and of fractures of the clavicle in the region of these joints. In treating severe sprains, subluxations and dislocations of the acromioclavicular joint he uses a modification of the Jones brachioclavicular splint. To avoid pressure phenomena about the elbow, the elbow is immobilized in a well padded right angle posterior metal splint. The sling, running from the elbow to the clavicle, is taken care of by a slotted piece of felt. Pressure downward on the clavicle is made by a padded strap running over the clavicle and around the chest, near the opposite axilla. Dislocations of the sternoclavicular joint are treated by means of the clavicular cross. If the condition is adequately treated, operation is unnecessary in most cases.

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33. Anderson, R.: Surg., Gynec. & Obst. **69**:770, 1939.
34. Howard, N. J.: Am. J. Surg. **46**:284, 1939.

External Dislocation of the Elbow.—Griesemer [35] reports 6 cases of a rare condition, external lateral dislocation of the elbow. In 4 of these the condition was partial luxation, and in 1 it was a subepicondylar complete dislocation. The injury may result from a fall on the outstretched hand, a fall on the inner side of the elbow or a direct blow on the forearm. The outstanding physical finding is a widening of the transverse diameter of the elbow joint. Complications of this injury may be Colles' fracture, fractures about the elbow, capsular and muscular lacerations, Volkmann's ischemic paralysis and neural and vascular injury. Reduction is usually obtained by manipulation with the patient under anesthesia. The forearm is manipulated into strong pronation; at the same time it is extended, and lateral flexion and supination are continued. The elbow is immobilized in a posterior plaster splint in flexion and supination. Dislocations over eight to ten days old are rarely reduced without operation. The writer advocates early active mobilization within twenty-four hours in cases of closed reduction and in thirty-six hours in cases of open reduction. Within three or four weeks satisfactory function should be obtained in uncomplicated cases.

Fractures of the Head of the Radius.—Discussing a group of 52 fractures of the head of the radius treated for the most part conservatively (only 3 were subjected to open operation), Bürmann [36] comments on the necessity for initial immobilization for at least two weeks. Of the 24 patients treated by very early motion and physical therapy, 17 were left with functional disturbances of various degree. Of 28 treated by primary immobilization for two weeks before institution of motion, 7 were left with functional disturbance. In general, the end results for all incomplete fractures and for complete fractures without dislocation were good. The results of the few complete or partial resections of the head of the radius were not satisfactory.

Isolated Fracture of the Capitulum and Trochlea Humeri.—Czembirek,[37] reporting 2 cases in which this fracture followed a fall on the extended arm, points out that the mechanism described by Böhler for this fracture, namely, a fall on the bent elbow with the arm in abduction, is not the only mechanism involved. In an 18 year old patient seen soon after injury, he removed the fragment. The result was a 30 degree limitation in flexion and a 30 to 40 degree limitation of extension. In a 15 year old patient he replaced the fragment. The result was full flexion with 40 degrees of limitation of extension.

Fracture of the Carpal Navicular Bone.—Cave [38] stresses the importance of early diagnosis and adequate early treatment of injuries to the

35. Griesemer, W. D.: Am. J. Surg. **47**:57, 1940.
36. Bürmann, E.: Arch. f. klin. Chir. **197**:115, 1939.
37. Czembirek, L.: Zentralbl. f. Chir. **66**:1086, 1939.
38. Cave, E. F.: The Carpus, with Reference to the Fractured Navicular Bone, Arch. Surg. **40**:54 (Jan.) 1940.

navicular bones. He believes that practically all navicular fractures heal if recognized and treated by early prolonged immobilization in plaster with the wrist in dorsal flexion and radial deviation. For nonunion the introduction of an autogenous bone graft through a drill hole in the bone, followed by prolonged fixation in plaster, seems to produce the most satisfactory results.

Slipped Femoral Epiphysis.—Ghormley and Fairchild [39] report the results of treatment of 55 patients with slipped upper femoral epiphysis. Twenty-six gave a definite history of severe injury to the hip. In 21 there was a gradual onset of symptoms. Males outnumbered females more than 3 to 1. Sixty-one per cent were normal or slightly above normal in weight. The age varied from 9 to 18, with the majority between 13 and 16 years. Some were adults with old deformities. Three patients were treated with a cast alone. Of these, 1 had a good result and 1 a fair result; the other was unchanged. Eight were treated by manipulation, with good results for 6, a fair result for 1 and a poor result for 1. Open reductions were done in 6 cases, with good results in 2, a fair result in 2, a poor result in 1 and an unknown result in 1. No internal fixation was used in 4 cases, and a bone screw was used in 1. Osteotomy of the femoral neck was done in 11 cases, in 7 without internal fixation, in 3 with beef bone screws and 1 with Kirschner wires. Of the patients in this group, 6 had good results; 3 had fair results; in the case of 1 it was too early to judge, and 1 was lost. In 12 cases of a preslipped stage of the disease, conservative treatment (splints, braces, crutches, physical therapy) was used. In 8 of these there were good results; in 2, fair results; in 1, poor results, and in 1, unknown results. The authors feel that early diagnosis and protection against further slipping by conservative measures can preserve a fairly normal hip. Closed reductions can be done only early and by the gentlest manipulation. In open operations when the epiphysis is not free they believe that a cuneiform osteotomy through the neck can be done with least damage to the epiphysis.

Fracture of the Femoral Neck Due to Metrazol Therapy.—Schizophrenic patients treated with metrazol have very severe muscular spasmodic contractions, which have been responsible for 23 fractures reported in the literature. (Eight were of the femoral neck, 2 bilateral.) Struppler [40] adds 2 more cases in which epileptiform convulsions of great severity resulted in fractures of the femoral neck requiring metallic fixation. He suggests that the patients be supported in bed with the hips and knees flexed during administration of the drug. He hopes that

39. Ghormley, R. K., and Fairchild, E. D.: Diagnosis and Treatment of Slipped Epiphyses, J. A. M. A. **114**:229 (Jan. 20) 1940.

40. Struppler, C.: Arch. f. klin. Chir. **197**:628, 1939.

this position of joint relaxations may minimize the effect of muscle contractions. Clinically, it apparently has made the cramps much easier to bear.

Ununited Fractures of the Femoral Neck in the Aged.—Gallie and Lewis [41] present their experience in the treatment of fractures of the femoral neck in the aged, based on 15 cases of use of a Smith-Petersen nail together with a bone graft. The technic consists of placing a nail close to the lower border of the neck, drilling a ½ inch (1.2 cm.) hole parallel to the nail in the upper portion of the neck and inserting a bone graft from the fibula or a suitable piece of bone from the crest of the ilium or the tibia. Union took place more slowly than in fresh fractures, but most of the patients were up in a chair in six months and walking after two or three months more.

Staple for Transverse Fractures of Long Bones.—Lexer and Large introduced a U-shaped nail, really a staple with an elongated central portion. Both limbs of the staple were sharpened for introduction into the shaft of the bone so as to bridge the break. Andreesen [42] has modified this staple and in addition fastens it to the bone by circular wire encompassing the bone above and below the fracture. It replaces a "Lane plate." The modified nail is three sided, has its ends shortened to 0.4 to 0.5 cm. and is notched in various places on its external surface to insure that the circular ties will stay in place.

Fractures of the Tibial Plateau.—Fractures of the tables of the tibia constitute about 3 per cent of fractures of the leg and may occur at any age after adolescence. Fractures of one table are more common than fractures of both tables, and 70 per cent involve the external table. The cause is usually indirect, the femoral condyle coming down on the tibial plateau with the knee in a valgus position. Central compressions probably result from the meniscuses taking the blow from the outer rim. Gerard-Marchant [43] divides these fractures into two types, separation fractures and compression fractures. A separation fracture is one in which the fractured table is separated from the main portion of the tibia, but without impaction. There are several types of separation fracture, depending on the point at which the fracture line enters the articular surface. The fragment may be displaced in any direction and is sometimes rotated. The compression type of fracture may consist of a central or a marginal depression, or the entire tuberosity may be impacted. A third type of fracture is a combination of the separation and compression fracture. There may be associated lesions, such as fractures of the tibia

41. Gallie, W. E., and Lewis, F. I.: J. Bone & Joint Surg. **22**:76, 1940.

42. Andreesen, R.: Zentralbl. f. Chir. **66**:1552, 1939.

43. Gerard-Marchant, P.: Rev. d'orthop. **26**:499, 1939.

tubercle, the tibial spine or the fibula. Ligamentous lesions usually involve the opposite lateral ligament. Cartilaginous injuries are frequent and are a major problem. Treatment consists of either closed or open reduction. There are several methods of closed reduction in common use. Manual reduction consisting of strong traction followed by adduction or abduction, combined with moldings, is often an efficient method. This will not be of any use in a centrally depressed fracture. Instrumental reduction is frequently utilized and may consist of traction by a Kirschner wire or the use of compressing instruments, mallets or Böhler's method of prying up the fragment by insertion of a nail. The last-mentioned method was not satisfactory in the author's hands. Fixation after closed reduction is usually by plaster, although some prefer continuous traction. For the latter method to be efficacious, the fragment under traction must be higher than the other, and the other fragment must be fixed by capsular or ligamentus attachment. Traction is of definite value in fractures of both tuberosities.

Open operation may be done either with or without opening of the knee joint. There are a great many incisions in use, but the surgeon should strive to get good exposure, particularly of the lower and posterior part of the fragment, in order to facilitate the repair. By doing an arthrotomy at the time of operation, the surgeon has the advantage of better visualization of the fragments and also the ability to inspect the meniscus. The latter is undoubtedly torn in many cases, and the diagnosis cannot be made without opening the joint. The opponents of arthrotomy raise the objection that opening the knee has special risks, and that it may be followed later by arthritis. In general, arthrotomy should be done if the fracture is complex, if the menicsus is suspected of being torn or if there is a tibial fragment in the joint.

Reduction of the fragments is often difficult even with wide exposure. The fragments may be solidly impacted and crushed together. The act of prying up the fragment may easily crush the spongy bone and create a large defect inferior to the raised fragment. The perfection of reduction should be judged by reestablishment of the articular surface. After reduction the fragments are never stable enough to leave without internal fixation. Various forms of internal fixation are in use. Nails do not hold well in the soft bone. If screws are used, they should be long and relatively thick. Two screws are better than one, and the fragment should be temporarily fixed with wires to prevent displacement while the screw is being inserted. Bone grafts may also be used for fixation. Grafts do not give as firm fixation as does metal, and they are useless for the separation fracture. Bone grafts have their greatest usefulness in the impacted fractures, in order partly to fill the defect remaining after reduction.

ORTHOPEDIC OPERATIONS

Reconstructive Operations for Septic Arthritis of the Hip Joint.—Hallock [44] presents end result studies on 38 patients who had 46 operations for reconstruction or stabilization of a hip joint that had been damaged or destroyed by previous suppurative arthritis. There were 20 reconstructions, 4 arthroplasties, 7 shelf stabilizations and 15 fusions. The results indicate that reconstructive procedures in children generally control dislocation and eliminate pain but leave considerable limitation of motion. Pain is likely to develop in adult life because of poor mechanics. Arthroplasties may prevent late development of pain, but many patients do not have enough residual bone for this type of procedure. Well constructed and well placed shelves, unless absorption ensues, will provide dislocated hips with stability and fairly good ranges of motion. Fusions, however, can be relied on to provide stable hips free from pain and without marked limp unless poor position is obtained or there is too much shortening. Early diagnosis and drainage of septic hips will decrease the necessity for reconstruction operations. If operations are to be done, it is advisable to wait two to three or more years after cessation of all drainage or other evidence of activity.

Excision of the Patella for Arthritis of the Knee Joint.—Berkheiser [45] discusses the morphology and comparative anatomy of the patella and the role of the patella in the mechanism of the knee joint. He then presents a series of 11 cases in which the patella was excised for arthritis of the knee, the aim being to relieve the patient of pain on extension and to increase the range of motion. The operation and the postoperative care are described, and 2 cases are given in some detail. The results of this operation were satisfactory in 8 cases and only fair in 3, which were not well selected. In general there was relief of pain and increase in function.

Lengthening of the Tibia and Fibula.—Abbott and Saunders [46] report on the further development of lengthening of the tibia and fibula. There are certain patients in whom epiphysial arrest is no longer applicable, because they have reached maturity. There are others, of short stature, in whom further reduction in height is undesirable, especially patients with marked degree of shortening; furthermore, it is to be borne in mind that shortening of the leg is carried out on the sound limb and on this ground may be objected to by the patient. Such indications,

44. Hallock, H.: Reconstructive and Stabilizing Surgery for Residual Suppurative Arthritis of Hip Joint: Study of Forty-Six Unselected Cases, J. A. M. A. **113**:2398 (Dec. 30) 1939.

45. Berkheiser, E. J.: Excision of Patella in Arthritis of Knee Joint, J. A. M. A. **113**:2303 (Dec. 23) 1939.

46. Abbott, L. C., and Saunders, J. B. de C. M.: Ann. Surg. **110**:961, 1939.

the authors feel, make it desirable to retain the procedure of leg lengthening for a limited group and prompted them to do further studies with a view to reducing the chances of complications. Among the complications were: deformities of the knee and of the ankle; malunion or nonunion; limitation of joint motion; muscle weakness; neural and circulatory disturbances; infection, and aseptic necrosis. To overcome these difficulties they describe an operation based on new principles. These involve complete division of the deep fasciae of the leg, the intermuscular septums and the interosseus membrane, as well as freeing of all the important blood vessels and nerves at the upper portion of the leg. Special osteotomies have been devised to retain the maximum portion of the origin of the muscles. A new apparatus has been used, which, they believe, gives better control of the fragments and offers less chance of infection of the pin wounds. They emphasize that the operation of leg lengthening is and in all probability always will be a major undertaking, with the possibility of serious complications. The procedure demands an intimate knowledge of anatomy and a careful study of every stage of the operation and postoperative care. The report covers 7 cases of treatment by the new method.

Fusion of the Ankle.—King [47] reports the results of ankle fusion in 106 patients operated on at the New York Orthopedic Dispensary and Hospital from 1934 to 1938 inclusive. In 72 patients ankle fusion was performed for paralytic drop foot. In 66 of these patients a subtalar triple arthrodesis had been carried out previously for lateral instability of the foot. In 19 of 23 patients with drop foot and unstable knee the knee was stabilized by ankle fusion. Ankle fusion was performed in 34 cases for paralytic calcaneous deformities. In 9 of these the patients also had an unstable knee; in 8 the knee was stabilized by ankle fusion. In 85 cases, or 80 per cent, the end result was considered good. In 10 cases, or 9 per cent, it was only fair. In no case was the result considered poor. The author recommends fusion in 5 to 10 degrees of equinus for males and 10 to 15 degrees of equinus for females.

Correction of Congenital Subluxation of the Fifth Toe.—Congenital varus deformity of the fifth toe with subluxation of the fifth metatarsophalangeal joint appeared in 60 cases during the past five years at the New York Orthopedic Dispensary and Hospital. Lantzounis [48] has performed 25 operations to correct this condition. Excellent results were obtained in 16, good results in 4 and poor results in 3. One patient was not seen after operation. One patient in the group in which the results were poor was operated on at the age of 2 years, which the author

47. King, B. B.: Ankle Fusion for Correction of Paralytic Drop Foot and Calcaneus Deformities, Arch. Surg. **40**:90 (Jan.) 1940.

48. Lantzounis, L. A.: J. Bone & Joint Surg. **22**:147, 1940.

feels is too young. The operative technic consists of making a 2 inch (5 cm.) longitudinal incision over the dorsal aspect of the fifth metatarsophalangeal joint. The extensor digitorum longus tendon of the fifth toe is isolated and divided at the distal end of the incision. The periosteum of the distal end of the fifth metatarsol bone, the capsule and the periosteum of the proximal phalanx are incised longitudinally and are then elevated subperiosteally from the dorsal, lateral and medial surfaces, their plantar attachment being left undisturbed. A drill hole is made in the distal end of the fifth metatarsal bone, and the proximal portion of the previously severed tendon of the extensor digitorum longus muscle is threaded through and sutured back onto itself. A mattress suture is placed in the periosteocapsular flap; the toe is then plantar flexed, and the mattress suture is tied. As a result of the tension exerted by the periosteocapsular flap, the toe is then stable, occupying a normal position without support.

RESEARCH

Phosphatase Activity in Early Callus.—Tollman and his associates [49] studied the relation of blood phosphatase, tissue phosphatase, tissue calcium and tissue metabolism in a series of rabbits subjected to osteotomy of the radius. They found no definite relation between the level of blood phosphatase and the healing of fractures. There was an irregular increase in tissue phosphatase activity and calcium deposition with time. A close relation was found between the phosphatase activity of the callus and the amount of calcium deposition. There was an initial rise in tissue metabolism of the callus, followed by a fall.

Bone-Regenerating Activity of Periosteum.—Levander [50] attempted to find by animal experimentation what ability to form bone there was in the periosteum. In adult animals periosteum was removed and transplanted under the skin. In none of the 9 animals used was there any bone regeneration. In young animals, similar subcutaneous transplantations showed new bone formation in 33 per cent for homoimplantation in 6 animals and in 25 per cent for autoimplantation in 8 animals. The new bone develops out of newly formed mesenchymal tissue at the seat of implantation. Implantation of bone, periosteum and bone marrow in 11 animals subcutaneously led to the production of bone. Of 5 animals with autoimplantation, 2 showed bone regeneration. The author believes that some substance is liberated from living bone tissue which possesses the power of activating nonspecific mesenchymal tissue and causing it to become differentiated into cartilaginous or bony tissue. The cellular

49. Tollman, J. P.; Drummond, D. H.; McIntyre, A. R., and Bisgard, J. D.: Tissue Metabolism and Phosphatase Activity in Early Callus, Arch. Surg. **40**:43, (Jan.) 1940.

50. Levander, G.: Acta chir. Scandinav. **83**:1, 1939.

mesenchymal layer of the periosteum should be regarded as part of the bony tissue itself. Periosteum should be reserved as the term for the connective tissue membrane which at all ages surrounds all bony tissue.

Joint Cartilage Under Various Physiologic Demands.—Freund [51] presents a study of the response of cartilage to certain functional stimuli. The behavior of cartilage under ultraphysiologic conditions (increased pressure) and infraphysiologic conditions (disuse) is discussed. Both of these factors, a disuse and overuse, are analyzed in the case of an 18 year old patient with spastic quadriplegia and athetosis. Thorough macroscopic and microscopic studies of joint surfaces are made and compared with normal. Freund concludes that functional stimuli below or above the physiologic optimum, if active over a long period, are deleterious to joint cartilage. The damage does not remain limited to the joint cartilage in growing persons but draws the bony portion of the epiphysis into participation by stopping further enchondral ossification. Whether the pressure force is intense and working over a relatively short period or whether it is still within physiologic limits but of protracted or even continuous action, the result will be the same. The joint cartilage will lose its normal elasticity and will suffer irreparable damage. Any marked alteration of function for a long period is certain to lead to degenerative changes of joint cartilage and may be followed by the whole syndrome of fully developed arthritis deformans.

Transplanted Epiphysial Cartilage.—In an effort to lengthen bone, Bisgard [52] transplanted full segment thicknesses of epiphysial cartilage from the femur into the tibia, which had been divided transversely. The segments consisted of epiphysial cartilage plate with adjacent bone and constituted less than half of the plate. Eight goats approximately 1 month old were used. One animal lost its leg as a result of circulatory interference, and 1 had an infected wound with loss of the graft. In the remaining 6 goats union occurred. The animals were observed for three months. All growth took place at the epiphysial ends. In no instance was length gained at the site of bisection. In fact, there was preliminary shortening from absorption either of bone at the severed ends of the tibia or of cartilage of the graft.

Lymph Spaces of Normal and Diseased Meniscus.—Fifty-three studies of the vascular supply of the meniscuses indicate they are avascular save for the anterior and posterior ends of their attachment. They rely on the lymphatics for resorption and are provided with long broomlike strands of lymphatics, which follow the course of the fibers

51. Freund, E.: Joint Cartilage Under Infraphysiologic, Ultraphysiologic and Euphysiologic Demands, Arch. Surg. **39**:596 (Oct.) 1939.

52. Bisgard, J. D.: Transplanted Epiphysial Cartilage, Arch. Surg. **39**:1028 (Dec.) 1939.

that make up the meniscus. They are demonstrated by the hydrogen peroxide method of Mangus, in which bubbles of gas liberated by the decomposing chemical as part of a catalytic reaction to tissue fluids fill the lymph channels and permit them to be studied. Rostock [53] reproduces studies of normal and abnormal lymph channels in degenerated and regenerating meniscuses. In a regenerated meniscus, apparently the lymph channels begin in time to approach the normal pattern as the tissues of the new meniscus respond to the demands of function.

[ED. NOTE: This is an interesting study. Too sweeping conclusions cannot be drawn from studies with hydrogen peroxide alone. Tissue spaces and blood vessels can be spread out by the catalytic action, and these can be confused with lymphatics.]

Pathologic Picture of Malacia of the Lunate Bone.—Nagura [54] working in Japan presents an interpretation of the zones of repair in cases of malacia of the lunate bone. In his opinion, he has found the key to the pathogenesis. He finds the areas similar to those associated with other aseptic necroses of bones. As the result of an injury, the articular cartilage and the spongiosa are broken, and a fissure extends into the spongiosa. Instead of the spongiosa healing with bone, chondroblasts from the cartilage-spongiosa boundary invade the cleft resulting from the trauma and go on to form a cartilage plane segregating the fracture area. This plane grows in thickness, and the fractured-off area protrudes into the joint space, where it is subjected consequently to further trauma. The bone is weakened, and the remaining bone breaks down under trauma. The areas of cartilage repair degenerate, and a giant cell, foreign body reaction type of repair follows, which marks the site of necrotization. Only the volar half of the bone remains. Pathologic sections are reproduced in support of his explanation of the course of events.

Effects on Ribs of Increased Intramedullary Pressure.—Using a modification of a method described by Larsen in 1938, Cressman and Blalock [55] present work which was carried out on the ribs of dogs. The experiments demonstrate that the cortex and the marrow may be killed and the periosteum separated by increased intramedullary pressure. In the absence of infection, periosteum is reattached and new bone is laid down, substituting the necrotic bone with sequestration. Non-toxin-producing organisms are well tolerated and result in hardly more alteration of the rib than does pressure alone. Toxin-producing staphylococci cause necrosis of bone and marrow and when combined with the necrosis succeeding on elevated intramedullary pressure cause extensive necrosis

53. Rostock, P.: Arch. f. klin. Chir. **197**:782, 1940.
54. Nagura, S.: Arch. f. klin. Chir. **197**:405, 1939.
55. Cressman, R. D., and Blalock, A.: Surgery **6**:535, 1940.

and sequestration which greatly resemble osteomyelitis in the human being. Necrosis of bone produced by elevated intramedullary pressure and the presence of virulent organisms, whether implanted directly or localized from the blood stream, leads to sequestration. The sequestrums, however, need not be extruded, as they are absorbed in situ.

Experimental Arthritis in Rabbits.—Cecil and his co-workers[56] report that they produced arthritis in rabbits with hemolytic streptococci and Streptococcus viridans introduced intravenously. They were able to produce arthritis by intravenous injection of Staphylococcus aureus, Bacillus paratyphosus A and Pneumococcus, but not with a number of other organisms which were tried. When streptococci were introduced into other sites, particularly the gums and sinuses, the animals had arthritis, depending on the degree of invasion of the blood stream and not from late dissemination of bacteria from an infected focus. Arthritis usually developed during the stage of bacteremia. Streptococci were repeatedly grown from the synovial fluid during the first two or three weeks after injection but seldom thereafter. The sedimentation rate was increased and the agglutinin titer elevated in a very high percentage of cases in which streptococci were injected. The pathologic changes taking place in the joint are described and are similar to the changes associated with rheumatoid arthritis in man. Although staphylococci produce marked suppuration in the joints, there was little difference in the pathologic picture after subsidence of the acute infection from that of arthritis produced with streptococci.

Notch Shadows in Lateral Roentgenograms.—In an anatomic study of the vertebral bodies of fetuses and newborn infants, Wagoner and Pendergrass[57] described the "notch" seen in lateral roentgenograms of the vertebral bodies. They found that the posterior "notch" shadow results from the presence of an actual indentation in the posterior wall of the body and is the point of entrance of the posterior arteries or veins. The anterior "notch" results from the presence of a large sinusoid space within the vertebra.

56. Cecil, R. L.; Angevine, D. M., and Rothbard, S.: Am. J. M. Sc. **198**:463, 1939.

57. Wagoner, G., and Pendergrass, E.: Am. J. Roentgenol. **42**:663, 1939.